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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Chlorinated Ethanes. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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CRITERIA DOCUMENT

CHLORINATED ETHANES

CRITERIA

Aquatic Life

The available freshwater data for chlorinated ethanes indicate that toxicity increases greatly with increasing chlorination, and that acute toxicity occurs at concentrations as low as 118,000 µg/l for 1,2-dichloroethane, 18,000 µg/l for two trichloroethanes, 9,320 µg/l for two tetrachloroethanes, 7,240 µg/l for pentachloroethane, and 980 µg/l for hexachloroethane. Chronic toxicity occurs at concentrations as low as 20,000 µg/l for 1,2-dichloroethane, 9,400 µg/l for 1,1,2-trichloroethane, 2,400 µg/l for 1,1,2,2-tetrachloroethane, 1,100 µg/l for pentachloroethane, and 540 µg/l for hexachloroethane. Acute and chronic toxicity would occur at lower concentrations among species that are more sensitive than those tested.

The available saltwater data for chlorinated ethanes indicate that toxicity increases greatly with increasing chlorination and that acute toxicity to fish and invertebrate species occurs at concentrations as low as 113,000 µg/l for 1,2-dichloroethane, 31,200 µg/l for 1,1,1-trichloroethane, 9,020 µg/l for 1,1,2,2-tetrachloroethane, 390 µg/l for pentachloroethane, and 940 µg/l for hexachloroethane. Chronic toxicity occurs at concentrations as low as 281 µg/l for pentachloroethane. Acute and chronic toxicity would occur at lower concentrations among species that are more sensitive than those tested.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of 1,2-dichloroethane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 9.4 µg/l, 0.94 µg/l, and 0.094 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 2,430 µg/l, 243 µg/l, and 24.3 µg/l, respectively.

For the maximum protection of human health from the potential carcinogenic effects due to exposure of 1,1,2-trichloroethane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 6.0 µg/l, 0.6 µg/l, and 0.06 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 418 µg/l, 41.8 µg/l, and 4.18 µg/l, respectively.

For the maximum protection of human health from the potential carcinogenic effects due to exposure of 1,1,2,2-tetrachloroethane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 1.7 µg/l, 0.17 µg/l, and 0.017 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 107 µg/l, 10.7 µg/l, and 1.07 µg/l, respectively.

For the maximum protection of human health from the potential carcinogenic effects due to exposure of hexachloroethane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 19 µg/l, 1.9 µg/l, and 0.19 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 87.4 µg/l, 8.74 µg/l, and 0.87 µg/l, respectively.

For the protection of human health from the toxic properties of 1,1,1-trichloroethane ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 18.4 mg/l.

For the protection of human health from the toxic properties of 1,1,1-trichloroethane ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 1.03 g/l.

Due to the insufficiency in the available data for monochloroethane, 1,1-dichloroethane, 1,1,1,2-tetrachloroethane, and pentachloroethane satisfactory criteria cannot be derived at this time, using the present guidelines.

INTRODUCTION

The chlorinated ethanes are produced in large quantities and used for production of tetraethyl lead and vinyl chloride, as industrial solvents, and as intermediates in the production of other organochlorine compounds. All of the chlorinated ethanes studied are at least mildly toxic, toxicity increasing with degree of chlorination. Some have been found in drinking waters, in natural waters, and in aquatic organisms and foodstuffs.

There are nine chlorinated ethanes, the properties of which vary with the number and position of the chlorine atoms. In most cases, both water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Chloroethane is a gas at room temperature; hexachloroethane is a solid; the rest are liquids. All are sufficiently soluble to be of potential concern as water pollutants. The only member of the series with a specific gravity less than 1 is chloroethane (specific gravity 0.9214).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963), a characteristic property which could influence their persistences in water. All are very soluble in organic solvents (Lange, 1956). The chlorinated ethanes undergo the usual dehalogenation and dehydrohalogenation reactions of chlorinated aliphatic compounds in the laboratory (Morrison and Boyd, 1966).

Pearson and McConnell (1975) were unable to demonstrate microbial degradation of the chlorinated ethanes, but did report chemical degradation of chlorinated hydrocarbons.

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Kirk, R.E. and D. Othmer, (eds.) 1963. Encyclopedia of Chemical Technology. 2nd ed. John Wiley and Sons, Inc., New York.

Lange, N.A. (ed.) 1956. Handbook of Chemistry. 9th ed. Handbook Publishers, Inc., Sandusky, Ohio.

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Pearson, C.R. and G. McConnell. 1975. Chlorinated hydrocarbons in the marine environment. Proc. R. Soc. London, Ser. B. 189: 305.

Aquatic Life Toxicology*

INTRODUCTION

Acute and chronic toxicity data for freshwater and saltwater fish and invertebrate species and a variety of chlorinated ethanes demonstrate a direct relationship of toxicity and degree of chlorination. A typical increase in acute toxicity of about two orders of magnitude exists between 1,2-dichloroethane and hexachloroethane. Chronic values for the fathead minnow decrease (toxicity increases) about 40 times between these same compounds. This relationship is also true for bioconcentration factors in the bluegill with a gradual increase from 2 to 139 from 1,2-dichloroethane to hexachloroethane. Effects of salinity, temperature, or other water quality factors on the toxicity of chlorinated ethanes are unknown.

EFFECTS

Acute Toxicity

The 48-hour values for Daphnia magna tested under the same conditions (U.S. EPA, 1978) are (µg/l): 1,2-dichloroethane, 218,000; 1,1,2-trichloroethane, 18,000; 1,1,1,2-tetrachloroethane, 23,900; 1,1,2,2-tetrachloroethane, 9,320; petachloroethane, 62,900; and hexachloroethane, 8,070 (Table 1). The 48-hour LC_{50} value for 1,1,1-trichloroethane (Table 5) was greater than the highest exposure concentration, 530,000 µg/l (U.S. EPA, 1978). Adema (1978) studied the effects of feeding (algal suspension) and age (1 and 7 days old) on the toxicity of 1,1,2-trichloroethane to Daphnia magna. After 48-hours no difference was observed, with values of 43,000 µg/l for each of four tests using measured concentrations (Table 1).

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

A midge, Tanytarsus dissimilis, has also been tested and the 48-hour LC_{50} value for this species and hexachloroethane is 1,700 μg/l. This result is about one-fifth that for the same chemical and Daphnia magna. However, since the midge result was based on measured concentrations and that for Daphnia magna was not, this difference may be methodological rather than a difference in sensitivity.

Alexander, et al. (1978) conducted acute toxicity tests with the fathead minnow and 1,1,1-trichloroethane under static and flow-through conditions with unmeasured and measured concentrations, respectively (Table 1). The flow-through, measured LC_{50} value (52,800 μg/l) is about one-half that (105,000 μg/l) for the static, unmeasured LC_{50} value.

Using continuous-flow procedures and measured exposure concentrations, the fathead minnow have been exposed (U.S. EPA, 1980) to 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, pentachloroethane and hexachloroethane, the 96-hour LC_{50} values are 118,000, 81,700, 20,300, 7,300, and 1,530 μg/l, respectively.

All data reported for bluegill are from 96-hour static toxicity tests with unmeasured concentrations (Table 1). The 96-hour LC_{50} values for 1,2-dichloroethane were 550,000 μg/l (Dawson, et al. 1977) and 431,000 μg/l (U.S. EPA, 1978). The other bluegill 96-hour LC_{50} values were (μg/l): 1,1,1-trichloroethane, 69,700; 1,1,2-trichloroethane, 40,200; 1,1,1,2-tetrachloroethane, 19,600; 1,1,2,2-tetrachloroethane, 21,300; pentachloroethane, 7,240; and hexachloroethane, 980.

For the bluegill and the fathead minnow, the toxicity of chlorinated ethanes clearly increased as the chlorine content increased. For Daphnia magna, no clear relationship exists, although there is a rough trend toward greater toxicity with increased chlorination. The less chlorinated compounds seem to be more toxic to Daphnia magna than to bluegill, whereas the more heavily chlorinated compounds are more toxic to bluegill.

Mysid shrimp and sheepshead minnow, the only saltwater animal species studied, were similar in their sensitivities to the chlorinated ethanes tested in static tests, except for pentachloroethane (Table 1). For pentachloroethane and hexachloroethane, the LC_{50} values for mysid shrimp were lower than those for the freshwater species, Daphnia magna (Table 1). Under comparable tests conditions sensitivity to chlorinated ethanes generally increase as the degree of chlorination increased, similar to the trend found with the freshwater invertebrate and fish species.

Toxicity tests with the sheepshead minnow have been conducted with five chlorinated ethanes (Tables 1 and 5). All tests were conducted under static conditions and concentrations in water were not measured. The 96-hour LC_{50} values for sheepshead minnows ranged from 2,400 µg/l for hexachloroethane to 116,000 µg/l for pentachloroethane. The LC_{50} values for this saltwater fish do not correlate as well with the number of chlorine atoms as did the values for the bluegill (Table 1). When sensitivities of the bluegill and sheepshead minnow are compared for each of these chlorinated ethanes, the LC_{50} values differ by less than a factor of three, except for pentachloroethane values which differ by a factor of 16.

Chronic Toxicity

No freshwater invertebrate species has been tested under chronic exposure conditions for any chlorinated ethane. However, embryo-larval tests have been conducted with the fathead minnow and 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, pentachloroethane, and hexachloroethane (U.S. EPA, 1978, 1980). The chronic values for these compounds are 20,000, 9,400, 2,400, 1,100, and 540 µg/l, respectively (Table 2). When these values are divided by the appropriate 96-hour LC_{50} values, the resultant acute-chronic ratios range from 2.8 to 8.7.

Only one chronic value is available for any chlorinated ethane and saltwater organisms. The chronic value for the mysid shrimp and pentachloroethane is 281 µg/l and the acute-chronic ratio is 1.4 (Table 2).

Plant Effects

Ninety-six-hour EC_{50} tests (Table 3), using chlorophyll a and cell number as measured responses, were conducted with the green alga, Selenastrum capricornutum, with the following results (µg/l): 1,1,2,2-tetrachloroethane, 136,000 and 146,000, respectively; pentachloroethane, 121,000 and 134,000, respectively; and hexachloroethane, 87,000 and 93,000. The highest concentration of 1,1,1-trichloroethane tested, 669,000 µg/l, (U.S. EPA, 1978) was not high enough to obtain a 96-hour EC_{50} value (Table 5).

The effects of chlorinated ethanes on plants increased slightly as chlorination increased, but the effect was not as clear as demonstrated by the bluegill and fathead minnow data. The alga was approximately 7 to 15 times less sensitive than bluegill to a specific compound.

The saltwater alga, Skeletonema costatum, was as sensitive to 1,1,2,2-tetrachloroethane (Table 3) as the mysid shrimp and sheepshead minnow. The 96-hour EC_{50} value for growth, based on cell count, was 6,230 µg/l. The 96-hour EC_{50} values for cell number were 58,000 µg/l for pentachloroethane 7,750 µg/l for hexachloroethane. There are no data reported in the literature on effects of chlorinated ethanes on saltwater vascular plants.

Data for 1,2-dichloroethane and 1,1,1-trichloroethane indicate that those compounds are not very toxic to the alga, Skeletonema costatum (Table 5).

Residues

The chlorinated ethanes do not strongly bioconcentrate (Table 4), but do show an increased bioconcentration potential with increased chlorination, particularly for penta- and hexachloroethane. The following steady-state bioconcentration factors were measured for bluegill: 1,2-dichloroethane, 2; 1,1,1-trichloroethane, 9; 1,1,2,2-tetrachloroethane, 8; pentachloroethane, 67; and hexachloroethane, 139. All of the chlorinated ethanes have an elimiation half-life of less than two days as measured by whole body levels in exposed bluegill.

Miscellaneous

These data (Table 5) have been discussed previously.

Summary

In general, the toxicity of the chlorinated ethanes to freshwater organisms increases with increasing chlorination. The least chlorinated tested compound was 1,2-dichloroethane, for which the 50 percent effect concentrations for *Daphnia magna*, fathead minnow, and bluegill were in the range of 118,000 to 550,000 µg/l; the various trichloroethanes and tetrachloroethanes are generally intermediate in toxicity, and pentachloroethane and hexachloroethane are most toxic. The 50 percent effect concentrations for hexachloroethane and *Daphnia magna*, midge larvae, rainbow trout, fathead minnow, and bluegill are in the range of 980 to 8,070 µg/l. Embryo-larval tests have been conducted with 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, pentachloroethane, and hexachloroethane and the chronic values were 20,000, 9,400, 2,400, 1,100, and 540 µg/l, respectively. The range of acute-chronic ratios was 2.8 to 8.7. The range of 96-hour EC_{50} values for a freshwater alga were from 136,000 µg/l for 1,1,2,2-tetrachloroethane to 87,000 µg/l for hexachloroethane. The chlorinated ethanes do not bioconcentrate in the bluegill to any great extent, although the effect of a chlorination is apparent with bioconcentration factors increasing from two for 1,2-dichloroethane to 139 for hexachloroethane for a series of five compounds.

As with the freshwater toxicity tests with fish and invertebrate species, there was an increase in effects with the more highly chlorinated compounds for saltwater toxicity tests. Under comparable test conditions the 96-hour LC_{50} values for the mysid shrimp were in the range of 113,000 µg/l for 1,2-dichloroethane to 940 µg/l for hexachloroethane. For the sheepshead minnow, the range was from 70,900 µg/l for 1,1,1-trichloroethane to 2,400 µg/l for hexachloroethane. Only one chronic value has been determined for the chlorinated ethanes and saltwater species and the chronic value for pentachloroethane and the mysid shrimp is 281 µg/l. The 96-hour EC_{50} values for a saltwater alga ranged from 6,230 to 58,200 µg/l.

CRITERIA

The available freshwater data for chlorinated ethanes indicate that toxicity increases greatly with increasing chlorination and that acute toxicity occurs at concentrations as low as 118,000 µg/l for 1,2-dichloroethane, 18,000 µg/l for two trichloroethanes, 9,320 µg/l for two tetrachlorethanes, 7,240 µg/l for pentachloroethane, and 980 µg/l for hexachloroethane. Chronic toxicity occurs at concentrations as low as 20,000 µg/l for 1,2-dichloroethane, 9,400 µg/l for 1,1,2-trichloroethane, 2,400 µg/l for 1,1,2,2-tetrachloroethane, 1,100 µg/l for pentachloroethane, and 540 µg/l for hexachloroethane. Acute and chronic toxicty would occur at lower concentrations among species that are more sensitive than those tested.

The available saltwater data for chlorinated ethanes indicate that toxicity increases greatly with increasing chlorination and that acute toxicity to fish and invertebrate species occurs at concentrations as low as 113,000 µg/l for 1,2-dichloroethane, 31,200 µg/l for 1,1,1-trichloroethane, 9,020 µg/l for 1,1,2,2-tetrachloroethane, 390 µg/l for pentachloroethane, and 940 µg/l for hexachloroethane. Chronic toxicty occurs at concentrations as low as 281 µg/l for pentachloroethane. Acute and chronic toxicity would occur at lower concentrations among species that are more sensitive than those tested.

Table 1. Acute values for chlorinated ethanes

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, U	1,2-dichloroethane	218,000	218,000	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	1,1,2-trichloroethane	18,000	-	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, M	1,1,2-trichloroethane	43,000	-	Adema, 1978
Cladoceran, *Daphnia magna*	S, M	1,1,2-trichloroethane	43,000	-	Adema, 1978
Cladoceran, *Daphnia magna*	S, M	1,1,2-trichloroethane	43,000	-	Adema, 1978
Cladoceran, *Daphnia magna*	S, M	1,1,2-trichloroethane	43,000	36,000	Adema, 1978
Cladoceran, *Daphnia magna*	S, U	1,1,1,2-tetrachloroethane	23,900	23,900	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	1,1,2,2-tetrachloroethane	9,320	9,320	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	pentachloroethane	62,900	62,900	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	hexachloroethane	8,070	8,070	U.S. EPA, 1978
Midge, *Tanytarsus dissimilis*	S, M	hexachloroethane	1,700	1,700	U.S. EPA, 1980
Rainbow trout, *Salmo gairdneri*	FT, M	hexachloroethane	980	980	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	FT, M	1,2-dichloroethane	118,000	118,000	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	S, U	1,1,1-trichloroethane	105,000	-	Alexander, et al. 1978

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	FT, M	1,1,1-trichloroethane	52,800	52,800	Alexander, et al. 1978
Fathead minnow, *Pimephales promelas*	FT, M	1,1,2-trichloroethane	81,700	81,700	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	FT, M	1,1,2,2-tetrachloroethane	20,300	20,300	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	FT, M	pentachloroethane	7,300	7,300	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	FT, M	hexachloroethane	1,530	1,530	U.S. EPA, 1980
Bluegill, *Lepomis macrochirus*	S, U	1,2-dichloroethane	550,000	-	Dawson, et al. 1977
Bluegill, *Lepomis macrochirus*	S, U	1,2-dichloroethane	431,000	489,000	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,1,1-trichloroethane	69,700	69,700	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,1,2-trichloroethane	40,200	40,200	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,1,1,2-tetrachloroethane	19,600	19,600	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,1,2,2-tetrachloroethane	21,300	21,300	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	pentachloroethane	7,240	7,240	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	hexachloroethane	980	980	U.S. EPA, 1978

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	S, U	1,2-dichloroethane	113,000	113,000	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	1,1,1-trichloroethane	31,200	31,200	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	1,1,2,2-tetrachloroethane	9,020	9,020	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	pentachloroethane	5,060	-	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	FT, M	pentachloro-	390	390	U.S. EPA, 1979
Mysid shrimp, *Mysidopsis bahia*	S, U	hexachloroethane	940	940	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,1,1-trichloroethane	70,900	70,900	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,1,2,2-tetrachloroethane	12,300	12,300	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	pentachloroethane	116,000	116,000	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	hexachloroethane	2,400	2,400	U.S. EPA, 1978

* S = static, FT = flow-through, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for chlorinated ethanes

Species	Method*	Chemical	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES			
Fathead minnow, *Pimephales promelas*	E-L	1,2-dichloroethane	14,000-29,000	20,000	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	E-L	1,1,2-trichloroethane	6,000-14,800	9,400	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	E-L	1,1,2,2-tetrachloroethane	1,400-4,000	2,400	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	E-L	pentachloroethane	900-1,400	1,100	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	E-L	hexachloroethane	410-700	540	U.S. EPA, 1978
		SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	LC	pentachloroethane	220-360	281	U.S. EPA, 1979

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* E-L = embryo-larval, LC = partial life cycle or full life cycle

Acute-Chronic Ratio

Species	Chemical	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Fathead minnow, *Pimephales promelas*	1,2-dichloroethane	20,000	118,000	5.9
Fathead minnow, *Pimephales promelas*	1,1,2-trichloroethane	9,400	81,700	8.7
Fathead minnow, *Pimephales promelas*	1,1,2,2-tetrachloroethane	2,400	20,300	8.5

Table 2. (Continued)

Acute-Chronic Ratio

Species	Chemical	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Fathead minnow, *Pimephales promelas*	pentachloroethane	1,100	7,300	6.6
Fathead minnow, *Pimephales promelas*	hexachloroethane	540	1,530	2.8
Mysid shrimp, *Mysidopsis bahia*	pentachloroethane	281	390	1.4

Table 3. Plant values for chlorinated ethanes (U.S. EPA, 1978)

Species	Chemical	Effect	Result (µg/l)
	FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	1,1,2,2-tetrachloroethane	Chlorophyll *a* 96-hr EC50	136,000
Alga, *Selenastrum capricornutum*	1,1,2,2-tetrachloroethane	Cell numbers 96-hr EC50	146,000
Alga, *Selenastrum capricornutum*	pentachloroethane	Chlorophyll *a* 96-hr EC50	121,000
Alga, *Selenastrum capricornutum*	pentachloroethane	Cell numbers 96-hr EC50	134,000
Alga, *Selenastrum capricornutum*	hexachloroethane	Chlorophyll *a* 96-hr EC50	87,000
Alga, *Selenastrum capricornutum*	hexachloroethane	Cell numbers 96-hr EC50	93,200
	SALTWATER SPECIES		
Alga, *Skeletonema costatum*	1,1,2,2-tetrachloroethane	Chlorophyll *a* 96-hr EC50	6,440
Alga, *Skeletonema costatum*	1,1,2,2-tetrachloroethane	Cell count 96-hr EC50	6,230
Alga, *Skeletonema costatum*	pentachloroethane	Chlorophyll *a* 96-hr EC50	58,200
Alga, *Skeletonema costatum*	pentachloroethane	Cell count 96-hr EC50	58,200
Alga, *Skeletonema costatum*	hexachloroethane	Chlorophyll *a* 96-hr EC50	8,570
Alga, *Skeletonema costatum*	hexachloroethane	Cell count 96-hr EC50	7,750

Table 4. Residues for chlorinated ethanes (U.S. EPA, 1978)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)
		FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	1,2-dichloroethane	2	14
Bluegill, *Lepomis macrochirus*	whole body	1,1,1-trichloroethane	9	28
Bluegill, *Lepomis macrochirus*	whole body	1,1,2,2-tetrachloroethane	8	14
Bluegill, *Lepomis macrochirus*	whole body	pentachloroethane	67	14
Bluegill, *Lepomis macrochirus*	whole body	hexachloroethane	139	28

Table 5. Other data for chlorinated ethanes (U.S. EPA, 1978)

Species	Chemical	Duration	Effect	Result (µg/l)
	FRESHWATER SPECIES			
Alga, *Selenastrum capricornutum*	1,1,1-trichloroethane	96 hrs	EC50 chlorophyll *a*	>669,000
Alga, *Selenastrum capricornutum*	1,1,1-trichloroethane	96 hrs	EC50 cell numbers	>669,000
Cladoceran, *Daphnia magna*	1,1,1-trichloroethane	48 hrs	EC50	>530,000
	SALTWATER SPECIES			
Alga, *Skeletonema costatum*	1,2-dichloroethane	96 hrs	EC50 chlorophyll *a*	>433,000
Alga, *Skeletonema costatum*	1,2-dichloroethane	96 hrs	EC50 cell count	>433,000
Alga, *Skeletonema costatum*	1,1,1-trichloroethane	96 hrs	EC50 chlorophyll *a*	>669,000
Alga, *Skeletonema costatum*	1,1,1-trichloroethane	96 hrs	EC50 cell count	>669,000
Sheepshead minnow, *Cyprinodon variegatus*	1,2-dichloroethane	96 hrs	LC50	>126,000 <226,000

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

Chloroethanes are hydrocarbons in which one or more of the hydrogen atoms have been replaced by a chlorine atom or atoms. Chloroethanes are widely used because of their low cost and properties which make them excellent solvents, degreasing agents, fumigants and cutting fluids. Some are used in the manufacture of plastics, textiles and in the synthesis of other chemicals. Around 1955, chloroethanes began to replace more toxic industrial solvents.

A large number of humans are industrially exposed to chloroethanes. In addition, the general population encounters these compounds in commercial products and as environmental contaminants resulting from industrial emissions including the discharge of liquid wastes.

Extensive literature has been generated by investigators who have studied the effects of chloroethanes on biological systems and the distribution of these compounds in the environment. The use of similar names for related chlorinated hydrocarbons has lead to possible confusion in the literature as to which compound elicited various toxicological effects.

Table 1 indicates the chemical names and some synonyms; Table 2 depicts the chemical structures of the chloroethanes. Chemical and physical properties of chloroethanes are listed in Table 3.

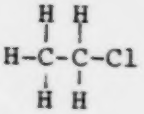
TABLE 1

Chloroethanes and Synonyms

Compound Name	Synonyms	
Monochloroethane	Chloroethane	Ethyl Chloride
1,1-Dichloroethane	Ethylidene Dichloride	EthylideneChloride
1,2-Dichloroethane	Ethylene Dichloride	Ethylene Chloride
1,1,1-Trichloroethane	Methyl Chloroform	Chlorothene
1,1,2-Trichloroethane	Ethane Trichloride	Vinyl Trichloride
1,1,1,2-Tetrachloroethane	Tetrachloroethane	
1,1,2,2-Tetrachloroethane	Acetylene Tetrachloride	Sym-Tetrachloroethane
Pentachloroethane	Pentalin	Ethane Pentachloride
Hexachloroethane	Perchloroethane	

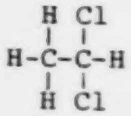
TABLE 2

Chloroethanes



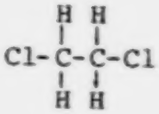
$$\begin{array}{c}H\ \ H\\ |\ \ |\\ H-C-C-Cl\\ |\ \ |\\ H\ \ H\end{array}$$

Monochloroethane



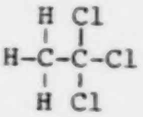
$$\begin{array}{c}H\ \ Cl\\ |\ \ |\\ H-C-C-H\\ |\ \ |\\ H\ \ Cl\end{array}$$

1,1-Dicholoroethane



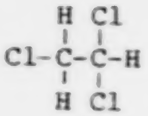
$$\begin{array}{c}H\ \ H\\ |\ \ |\\ Cl-C-C-Cl\\ |\ \ |\\ H\ \ H\end{array}$$

1,2-Dichloroethane



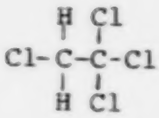
$$\begin{array}{c}H\ \ Cl\\ |\ \ |\\ H-C-C-Cl\\ |\ \ |\\ H\ \ Cl\end{array}$$

1,1,1-Trichloroethane



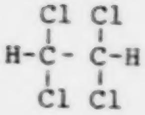
$$\begin{array}{c}H\ \ Cl\\ |\ \ |\\ Cl-C-C-H\\ |\ \ |\\ H\ \ Cl\end{array}$$

1,1,2-Trichloroethane



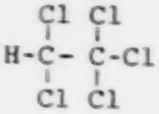
$$\begin{array}{c}H\ \ Cl\\ |\ \ |\\ Cl-C-C-Cl\\ |\ \ |\\ H\ \ Cl\end{array}$$

1,1,1,2-Tetrachloroethane



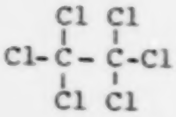
$$\begin{array}{c}Cl\ \ Cl\\ |\ \ |\\ H-C-\ C-H\\ |\ \ |\\ Cl\ \ Cl\end{array}$$

1,1,2,2-Tetrachloroethane



$$\begin{array}{c}Cl\ \ Cl\\ |\ \ |\\ H-C-\ C-Cl\\ |\ \ |\\ Cl\ \ Cl\end{array}$$

Pentachloroethane



$$\begin{array}{c}Cl\ \ Cl\\ |\ \ |\\ Cl-C-C-Cl\\ |\ \ |\\ Cl\ \ Cl\end{array}$$

Hexachloroethane

TABLE 3

Physical and Chemical Properties of Chloroethanes*

Compound	Formula Weight	Boiling Point °C	Melting Point °C	Specific Gravity[a]	Solubility In Water	Vapor Pressure (mm Hg)	Vapor Density[b]
monochloroethane	64.52	13.1	-138.7	0.9214	5.74 g/l	1,000 at 20°C	
1,1-dichloroethane	98.96	57.3	- 98	1.1776	5 g/l	230 at 25°C	
1,2-dichloroethane	98.96	83.4	- 35.4	1.253	8.1 g/l	85 at 25°C	3.42
1,1,1-trichloro-ethane	133.4	74.1	- 33	1.3492	0.48 g/l	96 at 20°C	4.55
1,1,2-trichloro-ethane	133.4	113	- 37.4	1.4405	Slightly soluble		
1,1,1,2-tetrachloro-ethane	167.9	129	- 68.1	1.5532	2.85 g/l		
1,1,2,2-tetrachloro-	167.9	146.3	- 36	1.596	2.9 g/l	16 at 25°C	5.79
pentachloroethane	202.3	162	- 29	1.6796	Insoluble		
hexachloroethane	236.7	186	- 187	2.091	Insoluble		

[a] At 20°C; Water = 1.00 at 4°C

[b] Air = 1.00

*Source:
Walter, et al. 1976
Price, et al. 1974
American Industrial Hygiene Association (AIHA), 1956; 1963
Weast, 1976

EXPOSURE

Ingestion from Water

The U.S. EPA (1974) identified a number of compounds in low concentrations in raw and finished waters of which approximately 38 percent were halogenated (U.S. EPA, 1976). Halogenated hydrocarbons have also been identified in 80 domestic water supplies by Symons, et al. (1975). Bellar, et al. (1974a) observed the highest concentration of organohalides in chlorinated finished water originating from surface water (37 to 150 mg/l). Among the compounds identified in raw or treated water are: 1,2-dichloroethane (Brass, et al. 1977); 1,1,1-trichloroethane (Kopfler, et al. 1976); in finished water, 1,1- and 1,2-dichloroethane, and 1,1,1-trichloroethane, (Coleman, et al. 1976); 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane (Keith, et al. 1976). Other reports of halogenated compounds in water or industrial waste water include the following: U.S. EPA., 1975a; Keith, 1972; Dowty, et al. 1975a,b; Bellar, et al. 1974b; Dietz and Traud, 1973.

Even though individual chemicals are frequently present in relatively small amounts in public water supplies, the potential toxicological implications are a matter of great concern. Of the 289 compounds identified in U.S. drinking water supplies (U.S. EPA, 1976), 21 were characterized as having carcinogenic activity (Kraybill, 1978). Of these 21, three were chloroethanes: 1,2-dichloroethane; 1,1,2-trichloroethane; tetrachloroethane (isomer not identified).

Monochloroethane is widely used as a solvent and in chemical synthesis (National Institute for Occupational Safety and Health (NIOSH), 1978c). No literature was found indicating the amounts discharged as liquid industrial wastes; however, monochloroethane has been identified in finished drinking water supplies (Kopfler et al., 1976). Brown, et al. (1975) reported that from six companies producing monochloroethane, 5.8 million pounds per year were lost into the environment from 575.5 million pounds produced; major losses would be into the atmosphere. Due to its low solubility in water (5.74 g/l), monochloroethane would be present only in water near point sources. In surface waters the compound would volatilize into the atmosphere.

1,1-Dichloroethane is not reported to be produced commercially in the United States (NIOSH, 1978c), but is imported for use as a solvent and cleaning agent in specialized processes. 1,1-Dichloroethane has been identified in the finished water of several metropolitan areas (Coleman, et al. 1976; Kopfler, et al. 1976).

More than 80 percent of the 1,2-dichloroethane produced in the United States is used to manufacture vinyl chloride and other chlorinated chemicals (U.S. EPA, 1975b); the solvent is also used in the manufacture of tetraethyl lead and as a constituent of many products used by the general public (U.S. EPA, 1975a). The gross annual discharge of 1,2-dichloroethane was estimated at 80 tons by the U.S. EPA (1975a). Nonpoint sources of 1,2-dichloroethane result from the use of products containing the compound, such as paint and varnish removers. The compound is difficult to degrade biologically (Price, et al. 1974), however, activated carbon filtration is 90 to 100 percent effective in removing the solvent from finished water (U.S. EPA, 1975a). Of 80 water supplies surveyed, 27 contained 1,2-dichloroethane at concentrations of 0.2 to 8 µg/l

(U.S. EPA, 1975c, 1974). In a separate survey, Symons, et al. (1975) reported that of 80 water supplies surveyed during the National Organics Reconaissance Survey for Halogenated Organics, only 32.5 percent contained detectable amounts of 1,2-dichloroethane, and the highest concentration found was 6.0 µg/l. The U.S. EPA (1979) concluded that 1,2-dichloroethane is not common in municipal water supplies, and when present, it is usually in neglible amounts; this compound is not usually present in ground water.

1,1,1-Trichloroethane is used primarily as a solvent, and as a cleaning and degreasing agent (Dow Chemical Co. 1969, 1973). The compound was found in the drinking water of three of five cities studied by Kopfler, et al. (1976). No information was found on the environmental fate in water or estimates of annual discharge as waste.

1,1,2-Trichloroethane is used in the manufacture of 1,1-dichloroethylene, as a solvent, and in organic synthesis. The gross annual discharge is estimated to be 2,000 tons. The compound is not produced by the biological decomposition of sewage or solid wastes or by incineration, but small amounts are formed by the chlorination process. 1,1,2-Trichloroethane persists in the environment (greater than two years) and is not degraded biologically; however, activated carbon filtration is reported to be 90 to 100 percent effective in removing the chloroethane from drinking water (U.S. EPA, 1975a). Of 10 water supplies surveyed by the U.S. EPA (1975a), only one contained 1,1,2-trichloroethane, while a second study of finished water from a metropolitan area, reported concentrations of 0.1 to 8.5 µg/l (U.S. EPA, 1975d).

1,1,1,2-Tetrachloroethane is used as a solvent and in the manufacture of a number of widely used products, (U.S. EPA, 1975a). It is potentially formed during chlorination of water (U.S. EPA, 1975a) and has been identified in finished water at a concentration of 0.11 µg/l (U.S. EPA, 1974).

1,1,2,2-Tetrachloroethane is used in the manufacture of 1,1-dichloroethylene, as a solvent, in the manufacture of, and as a constituent of many widely used products. The gross annual discharge from industrial sources was estimated to be 2,000 tons. The compound is not formed during biological decomposition of sewage or solid waste or by incineration, but may be formed during chlorination of treated sewage. The compound persists in the environment and is not degraded biologically but can be removed from drinking water by activated carbon filtration which is reported to be 90 to 100 percent effective (U.S. EPA, 1975a).

Apparently pentachloroethane is not produced commercially in the United States (NIOSH, 1978c) and is rarely found in drinking water.

Hexachloroethane is used in the manufacture of a number of products and the gross annual industrial discharge is estimated to be 2,000 tons. It is not formed in biological decomposition of wastes but can be produced in small quantities by chlorination of drinking water. The compound persists in the environment and is not degraded biologically (U.S. EPA, 1975a).

Analytical Techniques: Sensitive methods for identification of chlorinated ethanes and other organic compounds found in water, methods of quantitation, efficiency of sampling techniques and recovery were discussed by Keith, et al. (1976). Computerized gas chromatograph/mass spectrometry was presented as the best method available. There are many recent publications describing water sampling and analytical techniques for the identification of halogenated aliphatic hydrocarbons including the following: Dowty, et al. 1975b; Van Rossum and Webb, 1978; Lillian and Singh, 1974; Gough, et al. 1978; Glaze, et al. 1976; Deetman, et al. 1976; Coleman, et al. 1976; Fujii, 1977; Kopfler, et al. 1976; Cavallaro and Grassi, 1976; Nicholson and Meresz, 1975.

Ingestion from Food

The two most widely used solvents, 1,2-dichloroethane and 1,1,1-trichloroethane, are most often found in food. 1,1,1-Trichloroethane was found in small amounts as a contaminant in various food stuffs from the United Kingdom (Walter, et al. 1976). In meat, oils and fats, tea, and fruits and vegetables, amounts ranged from 1 to 10 μg/kg. Of the foods analyzed, olive oil contained the largest amount (10 μg/kg).

1,2-Dichloroethane is used in washing or lye peeling of fruits and vegetables (42 FR 29856) and represents a possible source in the diet of man. The volatile compound is also used as a fumigant in the storage of grain. Some fumigant can react with the grain to form nonvolatile residues; the health effects of these residues are not known (U.S. EPA, 1979). The amount of 1,2-dichloroethane remaining on grain after fumigation seems to depend on a number of factors, including grain type, grain size, storage conditions, and subsequent ventilation. Residues of 1,2-dichloroethane were not detected in wheat, flour, bran, middlings and bread (Berck, 1974).

However, using a different technique, in an earlier study, the same author found that 51 cereal grains sorbed from 0 to 84 percent of the applied dose, depending on the type and size of the grain (Berck, 1965, as cited in U.S. EPA, 1979). Because of the compounds volatility, only negligible amounts remain on foods prepared from treated grain (U.S. EPA, 1979).

1,2-Dichloroethane is commonly used as an extractant in the preparation of spice oleoresins. The dichloroethane isomer was detected in 11 of 17 spices in concentrations ranging from 2 to 23 ug of the compound per gram spice oleoresin (Page and Kennedy, 1975).

Concentrations of seven halogenated hydrocarbons were determined in various organs of three species of molluscs and five species of fish (Dickson and Riley, 1976). 1,1,1-Trichloroethane was found in the digestive tissue of one mollusc species (4 ng/g on a dry weight basis) and in three fish species where the compound was most strongly concentrated in the brain (4 to 16 ng) and gills (2 to 14 ng). No other data were found concerning the biological fate of chloroethanes in the food chain.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

Measured steady-state BCFs of 2, 9, 8, 67, and 139 were obtained for 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane, pentachloroethane, and hexachloroethane, respectively using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCFs for 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane, pentachloroethane, and hexachloroethane for the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans are calculated to be 1.2, 5.6, 5.0, 41.9, and 86.9, respectively.

No measured steady-state BCFs are available for 1,1,2-trichloroethane and 1,1,1,2-tetrachloroethane, but the equation

"Log BCF = (0.85 Log P) - 0.70" can be used (Veith, et al. 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids (Veith, 1980) from the octanol-water partition coefficients (P). Since no measured log P values could be found, log P values of 2.07 and 2.66 were calculated for 1,1,2-trichloroethane and 1,1,1,2-tetrachloroethane using the method described in Hansch and Leo (1979). Thus, the steady-state bioconcentration factors were estimated to be 11.5 and 36.4. An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCFs for 1,1,2-trichloroethane and 1,1,1,2-tetrachloroethane and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans are calculated to be 4.54 and 14.4, respectively.

Inhalation

Inhalation is the major route of exposure of humans to the volatile chloroethanes which are widely used as solvents, particularly in metal degreasing and dry cleaning operations. Many tons of chlorinated ethanes are reported to evaporate into the atmosphere (Kover, 1975; Murray and Riley, 1973). Inhalation exposure data for the general population are not available; however, some estimates can be made for occupational exposures. For example, health hazard evaluations of industries using 1,1,1-trichloroethane reported breathing zone concentrations ranging from 1.5 to 350 ppm (Table 4).

TABLE 4

Concentrations of 1,1,1-Trichloroethane Observed in Ambient Air of Various Industries

Concentration Range ppm	Concentration Range mg/m^3	Type of Job or Industry	Reference
4.0 - 37.0	21.8 - 201.7	Machining, Degreasing	Kominsky, 1976
2.5 - 79.5	13.6 - 433.4	Electrical Industry	Gilles, 1976
6.0 - 83.0	32.7 - 452.5	Electrical Industry	Gilles & Philbin, 1976
2.0 - 18.4	10.9 - 100.3	Manufacture Catapult Cylinders	Gilles & Rostand, 1975
36.5 - 159.5	199.0 - 869.6	Manufacture Rifle Scopes	Gunter, et al. 1977
73.0 - 350.0	398.0 - 1897	Degreasing-Cleaning	Gilles, 1977
1.5 - 16.6	8.18 - 90.5	Metal Industry	Levy & Meyer, 1977
12.0 - 118.0	65.4 - 643.3	Soldering-Degreasing	Gunter & Bodner, 1974

Dermal

Normally the skin is not a major route of exposure to chlorinated ethanes. As with most solvents, chloroethanes are absorbed through the skin, but in general, skin contact is avoided in the workplace and commercial products carry warnings. Most laboratory gloves are permeable to these solvents and should not be relied upon for protection (Sansone and Tewari, 1978).

PHARMACOKINETICS

Absorption

Monochloroethane is absorbed rapidly into the body following ingestion or inhalation (Sax, 1975) and has been used as an anesthetic (Merck, 1976). Absorption through the skin is minor.

Lethal amounts of 1,2-dichloroethane are absorbed following ingestion of a single dose (LD_{50} for rats, 0.97 mg/kg) or a single application to the skin (LD_{50} for rabbits, 3.89 mg/kg) (Smyth, et al. 1969). According to NIOSH (1978a) the effects of large doses of 1,2-dichloroethane are similar for all routes of entry.

Absorption of liquid 1,1,1-trichloroethane through the skin was studied by Stewart and Dodd (1964). Six subjects each immersed a thumb in a beaker of 1,1,1-trichloroethane for 30 minutes. Analysis of alveolar air collected during exposure at 10, 20 and 30 minutes indicated slow absorption (Table 5). In the workplace, dermatitis often results from skin contact with 1,1,1-trichloroethane (Gilles, 1977). The concentration of 1,1,1-trichloroethane in the blood of three victims of fatal intoxication (ingested or inhaled) has been reported to be 60, 62, and 120 ppm, respectively (Stahl, et al. 1969) indicating rapid absorption by both routes.

TABLE 5

Concentrations of 1,1,1-Trichloroethane Found in Alveolar Air of Experimental Subjects*

Duration of Thumb Immersion	Alveolar Air Concentrations (ppm)
10 minutes	0.10 - 0.10
20 minutes	0.14 - 0.37
30 minutes	0.19 - 1.02

*Source: Stewart and Dodd, 1964

A single application of 1 ml of 1,1,2-trichloroethane to the skin of guinea pigs was absorbed rapidly as indicated by the appearance of 3 to 4 µg/ml of the solvent in the blood in 30 minutes. After 12 hours, the blood concentration rose to almost 5 µg/ml (Jakobson, et al. 1977).

The absorption of inhaled 1,1,2,2-tetrachloroethane in humans was determined by Morgan, et al. (1970, 1972) using ^{38}Cl-labeled 1,1,2,2-tetrachloroethane. Volunteers deeply inhaled 2.5 mg of labeled vapor, held their breath for 20 seconds, exhaled through an activated-charcoal trap, inhaled room air, then exhaled through the trap a second time. Ninety-four to 97 percent of the inhaled tetrachloroethane was retained. Subjects continued to breathe room air and exhale for one hour through charcoal traps. Only 3.3 to 6 percent of the initially retained vapor (as ^{38}Cl) was exhaled one hour after the single inhalation exposure. Carbon dioxide was not monitored. Of a number of halogenated hydrocarbons tested (Morgan, et al. 1972), 1,1,2,2-tetrachloroethane had the highest partition coefficient (olive oil/gas, serum/gas), one of the highest rates of absorption (human inhalation of ^{38}Cl vapors) and one of the lowest rates of elimination by exhalation.

Distribution

In studying the metabolism of chloroethanes, Yllner (1971a,b,c,d,e) reported that 0.6 to 1.3 percent of an intraperitoneal (i.p.) dose of 1,2-dichloroethane (0.05 to 0.17 g/kg body weight) administered to mice was retained after 3 days. One to 3 percent of a dose of 1,1,2-dichloroethane (0.1 to 0.2 g/kg) was retained after three days. The highly toxic

1,1,2,2-tetrachloroethane (0.21 to 0.32 g/kg) was metabolized more slowly or stored, since 16 percent of the dose was retained 3 days after the dose was injected i.p. (Yllner, 1971d).

Holmberg, et al. (1977) studied the distribution of 1,1,1-trichloroethane in mice during and after inhalation. Solvent concentrations in the kidney and brain were about the same at a given exposure concentration, but concentrations in the liver were twice those observed in the kidney and brain following exposures to 100 ppm or more (Table 6). A pharmacokinetic model with both uptake and elimination of the first order best fit the empirical data. Hake, et al. (1960) reported that 0.09 percent of a large dose of 1,1,1-trichloroethane was retained in the skin of rats as the parent compound 25 hours after administration of an i.p. dose (700 mg/kg). The blood contained 0.02 percent, the fat 0.02 percent, and other sites 0.1 percent of the dose administered.

A study of solvents in post mortem human tissue was reported by Walter, et al. (1976). 1,1,1-Trichloroethane was found in body fat (highest concentration), kidney, liver, and brain. Data from autopsies of humans dying from acute exposures indicate that the highest tissue concentration was in the liver, followed by brain, kidney, muscle, lung, and blood (Stahl, et al. 1969).

In pregnant rats and rabbits, inhalation or ingestion of 1,1,1,2-tetrachloroethane resulted in the presence of high levels of the compound in the fetuses (Truhaut, et al. 1974).

Metabolism

In 1971, Yllner published a series of papers dealing with the metabolism of chloroethanes. Solvents were injected i.p. into mice

TABLE 6

Concentrations of 1,1,1-Trichloroethane in Tissues of Mice Following Inhalation Exposures*

Concentration ppm	Concentration mg/m^3	Exposure Time (h)	µg 1,1,1-Trichloroethane/g Tissue Blood	Liver	Kidney	Brain
10	54.2	24	0.6 ± 0.16[a]	1.5 ± 0.3	1.1 ± 0.2	0.8 ± 0.1
100	545.2	24	6.3 ± 3.0	12.2 ± 4.6	5.9 ± 2.2	6.2 ± 1.3
1,000	5452.0	6	36 ± 16	107 ± 38	60 ± 16	57 ± 17
5,000	27,260	3	165 ± 25	754 ± 226	153 ± 27	156 ± 24
10,000	54,520	6	404 ± 158	1429 ± 418	752 ± 251	739 ± 170

*Source: Holmberg, et al. 1977

[a] Values are means and standard deviations from 4 to 10 animals.

and the excretion of metabolites in the urine was monitored for three days. Table 7 summarizes Yllner's observations.

Metabolism of the highly toxic 1,1,2,2-tetrachloroethane, based on the identification of ^{14}C-labeled metabolites in the urine of mice (Yllner, 1971d), involved a stepwise hydrolytic cleavage of the chlorine-carbon bonds yielding glyoxalic acid and carbon dioxide. Nonenzymatic oxidation of 1,1,2,2-tetrachloroethane may produce a small amount of tetrachloroethylene. The parent compound may be dehydrochlorinated to form small amounts of trichloroethylene, a precursor to trichloroacetic acid and trichloroethanol.

The metabolism of pentachloroethane in the mouse is postulated to proceed at least partly through trichloroethylene and its metabolite chloral hydrate. The latter compound could also be formed from pentachloroethane by hydrolytic fission of carbon-chlorine bonds (Yllner, 1971e).

In Yllner's experiments, the percentage of the dose metabolized decreased with an increasing dose (1971a,b,c,d,e), suggesting that degradative pathways become saturated and an increasing amount is expired unchanged or retained in the body.

Ikeda and Ohtsuji (1972) exposed rats by inhalation to 200 ppm chloroethanes (1,1,1-tri; 1,1,2-tri; 1,1,1,2-tetra; or 1,1,2,2-tetrachloroethane) for eight hours and collected the urine for 48 hours from the beginning of exposure. Equimolar amounts of the same four solvents were injected i.p. into rats. Metabolites in the urine following inhalation or i.p. administration of all four solvents were trichloroacetic acid (TCA) and trichloroethanol(TCE) (Table 8), although relative amounts varied with the individual

TABLE 7

Major Metabolites of Chloroethanes in Mice*

Compound	Dose (g/kg)	Urinary Metabolites		
		Total %	Identified	% of Dose
1,2-Dichloroethane (^{14}C-)	12-15	51-73	S-carboxymethylcysteine	44-46 Free 0.5-5 Bound
			Thiodiacetic acid	33-44
			Chloroacetic acid	6-23
			2-Chloroethanol	0.0-0.8
			S,S'-ethylene-bis-cysteine	0.7-1.0
1,1,2-Trichloroethane (^{14}C-)	10-13	6-9	S-carboxymethylcysteine	29-46 Free 3-10 Bound
			Chloroacetic acid	6-31
			Thiodiacetic acid	38-42
			2,2-Dichloroethanol	
			2,2,2-Trichloroethanol	
			Oxalic acid	
			Trichloroacetic acid	
1,1,1,2-Tetrachloroethane		~17-49	Trichloroethanol	17-49
			Trichloroacetic acid	1-7
1,1,2,2-Tetrachloroethane (^{14}C-)	0.21-0.32	23-34	Dichloroacetic acid	
			Trichloroacetic acid	
			Trichloroethanol	
			Oxalic acid	
			Glyoxylic	
			Urea	
			Half of urinary activity not accounted for	
Pentachloroethane	1.1-1.8	87.3	Trichloroethanol	16-32
			Trichloroacetic acid	9-18
			Expired air contained trichloroethylene (2-16%) and tetrachloroethylene (3-9%)	

*Source: Yllner, 1971a, b, c, d, and e

TABLE 8

Urinary Metabolites from Wistar Rats Exposed to Solvents*

Solvent	No. of Experiments	Urinary Metabolites[a] (mg/kg body weight)	
		TCA	TCE
Inhalation[b] 200 ppm 8 hrs.			
1,1,1-Trichloroethane	8	0.5 ± 0.2	3.1 ± 1.0
1,1,2-Trichloroethane	8	0.3 ± 0.1	0.3 ± 0.1
1,1,1,2-Tetrachloroethane	8	39.4 ± 5.0	159.6 ± 24.4
1,1,2,2-Tetrachloroethane	8	1.7 ± 0.9	6.5 ± 2.7
Intraperitoneal[c] 2.78 mmol per kg body weight			
1,1,1-Trichloroethane	8	0.5 ± 0.2	3.5 ± 1.4
1,1,2-Trichloroethane	8	0.4 ± 0.1	0.2 ± 0.1
1,1,1,2-Tetrachloroethane	8	16.9 ± 1.6	97.3 ± 8.1
1,1,2,2-Tetrachloroethane	8	1.3 ± 0.2	0.8 ± 0.4

*Source: Ikeda and Ohtsuji, 1972

[a] numbers represent mean ± std. dev.

[b] Six rats per group

[c] Five rats per group

solvent. Metabolites were determined colorimetrically by the Fujiwara reaction; trichloroethanol was determined as the difference between the total trichlorocompounds and trichloroacetic acid.

Truhaut (1972) identified metabolites in the urine of rats, rabbits and guinea pigs given oral doses of 1,1,1,2-tetrachloroethane. His results indicate that the solvent is metabolized to trichloroethanol and excreted in the urine as trichloroethyl-β-D-glucuronic acid. In rats, small amounts of trichloroacetic acid were also formed.

Van Dyke and Wineman (1971) investigated the enzymatic dechlorination of a series of chloroethanes by rat liver microsomes (Table 9). The system required NADPH and oxygen and was induced by phenobarbitol and benzo(a)pyrene, but not by methylcholanthrene. Dechlorination of 1,1,2-trichloroethane was stimulated by addition of rat 100,000 x g supernatant to the microsomal assay (Gandolfi and Van Dyke, 1973).

1,1,2,2-Tetrachloroethane (437 mg/kg body weight) and hexachloroethane (615 mg/kg body weight) administered perorally to rats, decreased the cytochrome P-450 content and overall drug hydroxylation activity in the liver (Vainio, et al. 1976). Working with hepatic microsomes isolated from phenobarbital-induced rats, Ivanetich, et al. (1978), found that 1,1,1-trichloroethane and 1,2-dichloroethane degraded the heme moiety of cytochrome P-450; degradation appeared to require metabolic activation since NADPH was a requirement for binding.

In controlled human exposure studies, metabolism of inhaled 1,1,1-trichloroethane (70 ppm for 4 hours) represented 3.5 percent

TABLE 9

Dechlorination of Chloroethanes by Rat Liver Microsomes*

Compound[a]	Percent ^{36}Cl Enzymatically Removed[b]
Monochloroethane	<0.5
1,1-Dichloroethane	13.5
1,2-Dichloroethane	<0.5
1,1,1-Trichloroethane	<0.5
1,1,2-Trichloroethane	9.8
1,1,1,2-Tetrachloroethane	0.8
1,1,2,2,-Tetrachloroethane	6.0
Pentachloroethane	1.7
Hexachloroethane	3.9

*Source: Van Dyke and Wineman, 1971

[a] Uniformly labeled with chlorine-36

[b] Results are averages of duplicate assays from at least six rats

of total uptake (Monster, 1979). The author suggested that transformation of the parent compound takes place by hydroxylation to trichloroethanol, followed by partial oxidation of trichloroethanol to trichloroacetic acid.

Excretion

Yllner quantitated the excretory products of 1,2-di; 1,1,2-tri; 1,1,1,2-tetra; 1,1,2,2-tetra; and penta-chloroethane in mice (1971a,b,c,d,and e) (Table 10). Compounds were administered i.p. and excretion was monitored for 3 days; urinary metabolites are listed in Table 7.

More than 90 percent of the doses of 1,2-dichloroethane or 1,1,2-trichloroethane was excreted in the first 24 hours with more than half found in the urine. Seventy-eight percent of the 1,1,1,2-tetrachloroethane administered was excreted in 72 hours with 48 percent expired unchanged (21 to 62 percent). Eighty-four percent of the 1,1,2,2-tetrachloroethane dose was eliminated in 72 hours, with about half the dose lost as CO_2, and one-fourth excreted in the urine; approximately 16 percent remained in the animal. About one-third of the pentachloroethane dose was expired unchanged; the expired air also contained trichloroethylene (2 to 16 percent) and tetrachloroethylene (3 to 9 percent) indicating dechlorination of pentachloroethane. Twenty-five to 50 percent of the dose was excreted in the urine.

Stewart, et al. (1961, 1969, 1975) studied controlled human exposures to 1,1,1-trichloroethane vapor. The concentration of the unchanged solvent in the post-exposure expired air was predictable enough to estimate the magnitude of exposure. The rate of

TABLE 10

Excretion of Chloroethanes Administered to Mice*,a

Chloro-ethane Compound	Dose (g/kg)	Expired Unchanged (%)	Expired as CO_2 (%)	In Urine (%)	In Feces (%)
1,2-	0.05-0.17	10-45	12-15	51-73	0-0.6
1,1,2-	0.1 -0.2	6-9	10-13	73-87	0.1-2.0
1,1,1,2-	1.2 -2.0	21-62	-	18-56	-
1,1,2,2-	0.21-0.32	4	45-61	23-34	-
Penta-	1.1 - 1.8	12-51	-	25-50	-

*Source: Yllner, 1971a,b,c,d,e

[a] Intraperitoneal injection - Excretory products collected for 3 days

1,1,1-trichloroethane excretion was a function of exposure duration as well as concentration (Table 11).

Monster, et al. (1979) reported that 60 to 80 percent of 1,1,1-trichloroethane (70 or 140 ppm for 4 hours) inhaled by human volunteers was expired unchanged; two metabolites, trichloroethanol and trichloroacetic acid, excreted in the urine, represented approximately three percent of the total uptake. Although measurements of the parent compound and its metabolites are commonly used to estimate uptake of 1,1,1-trichloroethane, studies by Monster and Houtkooper (1979) have shown that the best estimates of uptake are provided by concentrations present in blood.

A multistage cryogenic trapping system was used to concentrate trace organic compounds in human respiratory gas: three chlorinated ethanes, 1,1,1-trichloroethane, 1,1- and 1,2-dichloroethane, were identified in the expired air of subjects with no known history of exposure (Conkle, et al. 1975). No estimates of half-lives and body burdens of chloroethanes were found in the literature. These data must be obtained, however, in order to identify populations at risk.

EFFECTS

Acute, Subacute, and Chronic Toxicity

A number of excellent publications are available which review the acute and chronic effects of some chloroethanes. Aviado, et al. (1976) published a monograph on "Methyl Chloroform and Trichloroethylene in the Environment." NIOSH (1978b) published criteria documents for recommended standards of occupational exposure to 1,1,1-trichloroethane (NIOSH, 1978b), 1,2-dichloroethane

TABLE 11

1,1,1-Trichloroethane Breath Concentrations of
Men and Women Exposed at 350 ppm*

Time	Men			Women		
	No.	Mean (ppm)	Range (ppm)	No.	Mean (ppm)	Range (ppm)
	Isolated 1-Hour Exposure					
2 Minutes pre-exit exposure	3	150	144 - 157	3	183	173 - 193
1 Minute post exposure	3	76.4	48.6 - 108	2	120	116 - 123
23 Hours post exposure	3	1.11	0.75 - 1.63	2	0.8	0.57 - 1.03
	Isolated 7.5 Hour Exposure					
2 Minutes pre-exit exposure	4	234	222 - 252	3	254	247 - 262
1 Minute post exposure	4	149	144 - 153	4	181	156 - 205
16 Hours post exposure	4	7.07	6.62 - 7.73	4	6.93	4.83 - 8.74

*Source: Stewart, et al. 1975

(NIOSH, 1976b), and 1,1,2,2-tetrachloroethane (NIOSH, 1976a). The U.S. EPA (1979) has recently published a comprehensive review of the health and environmental effects of 1,2-dichloroethane. A monograph prepared by Walter, et al. (1976) on chlorinated hydrocarbon toxicity, included 1,1,1-trichloroethane and was prepared for the Consumer Product Safety Commission, Bureau of Biomedical Science. A comprehensive review of 1,1,1-trichloroethane literature from 1953 through 1973 was conducted by the Franklin Institute Research Laboratories for the U.S. EPA (Kover, 1975).

Only a representative portion of the literature available on the toxic effects of chloroethanes will be discussed since the focus of this document is on the effects of chronic ingestion and possible carcinogenic effects.

Monochloroethane is considered one of the least toxic of the chloroethanes; however, as a halogen-containing hydrocarbon it is potentially damaging to the liver and is known to disturb cardiac rhythm (Goodman and Gilman, 1975). Overdoses of several volatile anesthetics including monochloroethane can lead to severe contractile failure of the heart (Doering, 1975). At the stage of maximal failure, the myocardial stores of ATP and phosphocreatine were increased indicating a reduction in the utilization of energy stores.

1,1-Dichloroethane is less toxic than the 1,2-isomer but the 1,1-isomer's use as an anesthetic was discontinued because of marked excitation of the heart (Browning, 1965). Liver injury has been reported in experimental animals (Sax, 1975) following acute exposures ranging from 4,000 to 17,500 ppm.

The U.S. EPA reports that 1,2-dichloroethane is toxic to humans by ingestion, inhalation, and absorption through skin and mucus membranes. Symptoms of 1,2-dichloroethane toxicosis include central nervous system depression, gastrointestinal upset, and systemic injury to the liver, kidneys, lungs, and adrenals (U.S. EPA, 1979). Smyth, et al.(1969) reported an oral LD_{50} for 1,2-dichloroethane in rats of 0.77 ml/kg (range 0.67 to 0.89) and a dermal LD_{50} for rabbits of 3.89 ml/kg (range 3.40 to 4.46). In both cases a single dose was administered.

Acute and subacute inhalation studies with dogs, rabbits, guinea pigs, rats and mice indicated that 1,2-dichloroethane was toxic to the liver, bone marrow, blood, kidneys, myocardium and sometimes the adrenals (Heppel, et al. 1946; Liola, et al. 1959; Liola and Fondacaro, 1959). Chronic inhalation exposures, 100 to 400 ppm, for 5 to 32 weeks in several species were reported to be toxic in the liver at 200 ppm and above (Spencer, et al. 1951; Hofmann, et al. 1971). Increased liver weights were observed in guinea pigs following a 32 week exposure to 100 ppm 1,2-dichloroethane (Spencer, et al. 1951).

DiVincenzo and Krasavage (1974) used ornithine carbamyl transferase (OCT) activity as a specific indication of the hepatotoxic properties of various organic solvents. Of the 33 solvents tested, 5 were chlorinated ethanes (1,1-; 1,2-; 1,1,1-; 1,1,2-; 1,1,2,2-). The solvents were injected intraperitoneally into mature naive male guinea pigs, and the serum OCT level was measured 24 hours later. Of the five chlorinated ethanes tested, only two (1,1,2- and 1,2-) showed an increase in serum OCT activity. 1,1,2-Trichloethane showed elevations in serum OCT activity at dosages of 200 and 400 mg/kg, indicating a moderate level of hepatotoxicity. Liver damage was confirmed by histological examination. 1,2-Dichloroethane showed an elevated OCT activity at 600 mg/kg, but not at 300 or 150 mg/kg, indicating a low level of hepatotoxicity. Liver damage was not confirmed by histological examination. The remaining chlorinated ethanes tested in this study (1,1,2,2-; 1,1,1-; and 1,1-) did not show elevated serum OCT activity or discernable hepatocellular damage. These data are summarized in Table 12.

Ingestion of 1,2-dichloroethane by man has often resulted in death which was usually ascribed to circulatory and respiratory failure. Brief descriptions of several cases are presented in Table 13. Clinical symptoms of toxicosis were usually present within 2 hours after ingestion. In addition to the signs and symptoms listed in Table 13, a reduction in clotting factors and platelet count were observed, and fibrinolysis was increased up to four times its normal value. Martin, et al. (1969) reported a "thrombin time" after fibrinogen substitution of 59 seconds as compared to the normal value of 12 seconds. Post mortem examinations usually revealed thrombi in the pulmonary arterioles and capillaries, hemorrhages into the mucosa of the esophagus, stump of the stomach, rectum, and myocardial tissues.

Patients suffering from acute 1,2-dichloroethane poisoning developed diffuse dystrophic changes in brain and spinal cord cells which were described clinically as toxic encephalomyelopathy (Akimov, et al. 1978). One man who survived acute poisoning suffered irreversible mental defects, acute liver dystrophy,

TABLE 12

Evaluation of Acute Hepatotoxic Properties of Organic Solvents*

Solvent	n[a]	Dose (mg/kg)	Mean Serum OCT activity (I.U.)[b]	Results	Relative Hepatotoxicity[c]
Tetrachloroethane[d] ($Cl_2CHCHCl_2$)	4	75	2.9	Lacks hepatotoxic properties, even at near lethal doses	None
	8	150	3.2		
	4	300	4.5		
1,1,1-Trichloroethane (Cl_3CCH_3)	4	75	0.9	Shows no acute hepatotoxic properties	None
	4	150	0.9		
	4	300	0.9		
	4	600	1.6		
1,1,2-Trichloroethane (Cl_2CHCH_2Cl)	4	200	47.3	elevation in serum OCT level does not appear to be dose-related; tissue necrosis seen at both doses; lipid deposition at higher dose	Moderate
	4	400	55.9		
1,1-Dichloroethane (Cl_2CHCH_3)	4	150	1.3	Histology normal; dosages failed to elicit a change in serum OCT activity	None
	4	300	1.8		
	4	500	1.2		
	4	750	3.2		
1,2-Dichloroethane[e] ($ClCH_2CH_2Cl$)	4	150	3.0	Liver damage indicated by serum OCT activity; elevation was not confirmed by histological examination	Low
	4	300	3.1		
	4	600	34.6		

*Source: DiVincenzo and Krasavage, 1974

[a] n = number of animals tested

[b] Serum OCT activity in healthy guinea pigs (117 animals tested) is 2.02 ± 1.61 with a range of 0-8.9

[c] Low indicates an elevated OCT at a dose 500 mg/kg

Moderate indicates an elevated OCT at dosages between 500 and 50 kg

None indicates that no OCT activity changes were noted at levels tested

[d] at 500 mg/kg, all 4 animals tested died

[e] at 600 mg/kg, 1 of 4 animals tested died

TABLE 13

Signs and Symptoms Following 1,2-Dichloroethane Ingestion

Author	Patient Data	Amount Consumed	Onset of Symptoms	Progression of Signs and Symptoms
Secchi, et al. (1968)	80-year-old	50 ml		Elevated serum enzymes - LDH, SGOT, SGPT, alkaline phosphatase, glutamic dehydrogenase, RNAase; death a few hours after ingestion.
Martin, et al. (1969)	57-year-old man	40 ml		Somnolence; vomiting; sinus tachycardia; ventricular extrasystoles; dyspenea; loss of blood pressure; cardiac arrest; death 24 hours after ingestion.
Schonborn, et al. (1970)	18-year-old man	50 ml	1 hour	Somnolent; cyanotic; shock of circulatory system; death after 17 hours in irreversible shock.
Yodaiken and Babcock (1973)	14-year-old boy	15 ml	2 hours	Headache; staggering; lethargy; periodic vomiting; blood pressure drop; cardiac arrest; pulmonary edema; refractory hypotension; death on sixth day.

nephropathy, and anemia (Dorndorf, et al. 1976). Acute poisoning also caused an elevation of leukocytes in the blood and protein in the urine (Bonitenko, et al. 1977).

The effects of acute inhalation exposures to 1,2-dichloroethane are similar to those observed after ingestion, with death being attributed to respiratory and circulatory failure. (Wendel, 1948; Wirtschafter and Schwartz, 1939; Troisi and Cavallazzi, 1961). Nonfatal acute exposures have also been reported (Wirtschafter and Schwartz, 1939; McNally and Fostedt, 1941). In a 1947 report, Rosenbaum reported that acute poisonings developed rapidly following repeated exposure of workers to concentrations of 75 to 125 ppm (Rosenbaum, 1947). Many persons exposed to lower concentrations of 1,2-dichloroethane reported delayed effects with the most severe reactions occurring after the evening meal (Byers, 1943).

Summaries of the acute effects of human exposures to 1,2-dichloroethane are similar for all routes of entry: ingestion, inhalation, and skin absorption. Such exposures result in nausea, vomiting, dizziness, internal bleeding, cyanosis, rapid but weak pulse, and unconsciousness. Acute exposures often lead to death from respiratory and circulatory failure. Chronic exposures to 1,2-dichloroethane have resulted in neurological changes, loss of appetite and other gastrointestinal problems, irritation of mucous membranes, liver and kidney impairment, and in some cases, death (NIOSH, 1978a; U.S. EPA, 1979).

The anesthetic properties of 1,1,1-trichloroethane have been demonstrated in rats (Torkelson, et al. 1958), mice (Gerhring, 1968), and dogs and monkeys (Krantz, et al. 1959). Based on minimum concentrations causing prostration in two hours, Lazarew (1929) determined that the 1,1,2-isomer was four times more toxic than the 1,1,1-isomer (Table 14).

Adams, et al. (1950) determined an LC_{50} for rats exposed up to seven hours by inhalation to 1,1,1-trichloroethane (contained up to one percent 1,1-dichloroethane). At 18,000 ppm, half of the animals were dead in three hours (2.1 to 4.2 hours, 95 percent confidence limits); at 14,250 ppm half the animals were dead in seven hours (12,950 to 15,675 ppm, 95 percent confidence limits).

Both commercial grade and 1,1,1-trichloroethane (no inhibitors) were administered orally to rats, mice, rabbits, and guinea pigs for determination of an LD_{50} for each species (Torkelson, et al. 1958). Single doses of undiluted solvent were given by gavage (Table 15). No differences were observed in toxic responses of animals to solvents of varying purity.

During 1,1,1-trichloroethane anesthesia of dogs, two of the animals died suddenly (Rennick, et al. 1949). Further inhalation experiments indicated that at 0.33 to 0.53 g/kg, the solvent sensitized the heart to epinephrine-induced ventricular extrasystoles and ventricular tachycardia. Cardiac sensitization, an increased susceptibility of the heart to catecholamines, is induced by a number of halogenated hydrocarbons (Reinhardt, et al. 1973).

Electrocardiogram changes in three dogs were observed after an abrupt drop in blood pressure induced by 1,1,1-tricholoroethane anesthesia (Griffiths, et al. 1972). Dogs were sedated with sodium pentobarbital (20 mg/kg) before administration of about 125,000 ppm

TABLE 14

Effects of Trichloroethane Isomers on Mice*

Isomer	Minimum Concentration for Response within 2 Hours of Exposure (mg/l)		
	proneness	loss of reflexes	death
1,1,1-	40	45	65
1,1,2-	10	15	60

*Source: Lazarew, 1929

TABLE 15

LD_{50} After Oral Administration of 1,1,1-Trichloroethane in Laboratory Animals[*,a]

Characteristics of 1,1,1-Trichloroethane	Animal Sex/Species	LD_{50} (g/kg) Mean	LD_{50} (g/kg) 95% Confidence Limits
2.4-3.0% dioxane	35 male rats	12.3	11.0-13.7
0.12-0.3% butanol	35 female rats	10.3	8.3-12.8
Trace of 1,2-dichloroethane	16 female mice	11.2	---
"	16 female rabbits	5.7	3.5-9.4
"	16 male guinea pigs	9.5	3.5-13.3
Uninhibited	40 male rats	14.3	12.1-17.0
Not further defined	50 female rats	11.0	9.5-13.0
"	40 female mice	9.7	---
"	40 female rabbits	10.5	9.7-11.3
"	30 male guinea pigs	8.6	6.1-12.2

*Source: Torkelson, et al. 1958

[a] Administered undiluted by gavage

1,1,1-trichloroethane. Krantz, et al. (1959) noted a drop in blood pressure to about one-half of its normal value prior to respiratory failure in 11 dogs and 10 monkeys administered 0.60 ml/kg and 0.59 ml/kg, respectively. EKG abnormalities were also noted.

Recent studies have demonstrated a relationship between changes in cardiovascular parameters and exposure to 1,1,1-trichloroethane including the following: Herd, et al. (1974) observed a dose-dependent two-phase drop in blood pressure and decreased peripheral resistance following an inhalation exposure in dogs; also in dogs, Reinhardt, et al. (1973) found 27.8 mg/l to be the minimum concentration causing sensitization of the heart to epinephrine-induced arrhythmias; Clark and Tinston (1973) reported the effective concentration for sensitization to be 40.7 mg/l in another group of dogs; in mice, Aviado and Belej (1974) noted arrhythmias during inhalation of 2.2×10^6 mg/m^3 1,1,1-trichloroethane.

In summary, inhalation of 1,1,1-trichloroethane by various species of animals induces toxic effects in the central nervous, cardiovascular, and pulmonary systems, and in the liver and kidney (Truhaut, et al. 1973; Horiguchi and Horiguchi, 1971; Tsapko and Rappoport, 1972; Belej, et al. 1974; Herd, et al. 1974; Torkelson, et al. 1958; MacEwen and Vernot, 1974). In most animal studies, high concentrations were used. In the experiments cited, the lowest concentration producing toxic effects was 73 ppm, administered four hours per day from 50 to 120 days (Tsapko and Rappoport, 1972).

The effects most often reported following 1,1,1-tricholorethane exposure of humans are central nervous system disorders. These include changes in reaction time, perceptual speed, manual dexterity, and equilibrium; however, cardiovascular effects have not been observed at the concentrations used in human exposures. Inhalation exposures of 450 ppm for eight hours caused eye, nose, and throat irritation, and decreased perceptive capabilities under stress conditions (Salvini, et al. 1971). Perceptual speed, reaction times, and manual dexterity were impaired in volunteers inhaling 350 ppm for three hours; impairment was not evident following inhalation of 250 ppm for two hours (Gamberale and Hultengren 1973). Two of 11 men inhaling 500 ppm 1,1,1-trichloroethane for 6.5 to 7 hours/day for five days showed abnormal results in a modified Romberg's test (Stewart, et al. 1961).

An epidemiologic study of 151 matched pairs of employees was conducted in two adjacent textile plants, one of which used inhibited 1,1,1-trichloroethane as a general cleaning solvent (Kramer, et al. 1976). Employees in the study population had exposures to the solvent for six years or less at varying concentrations measured by breathing zone sampling and personal monitoring techniques. The eight hour time-weighted average of personal sampling concentrations ranged from 4 ppm to 217 ppm. Cardiovascular and hepatic observations were of primary interest. Statistical analysis of the data did not reveal any clinically pertinent findings which were associated with exposure to 1,1,1-trichloroethane.

A dermal LD_{50} for 1,1,2-trichloroethane in rabbits was reported to be 3.73 ml/kg body weight; an ingestion LD_{50} for rats was reported to be 0.58 ml/kg; for inhalation, an 8-hour exposure at 500 ppm was fatal to four of six rats (Smyth, et al. 1969).

LD_{50} concentrations of 1,1,2-trichloroethane (0.35 ml/kg in mice and 0.45 ml/kg in dogs, i.p.) caused kidney necrosis (Klaassen and Plaa, 1967). The effective dose for 50 percent of the animals (ED_{50}) which produced kidney necrosis was 0.17 ml/kg in mice and 0.4 ml/kg in dogs, examined 24 hours after receiving the compound. Forty-eight hours after receiving an ED_{50} dose, (0.35 ml/kg, i.p.), the livers of treated dogs exhibited centrolobular necrosis as indicated by elevated serum glutamate pyruvate transaminase (SGPT) levels.

Acute exposures of mice by inhalation to vapors of 1,1,2-trichloroethane (3750 ppm for 30 minutes) produced a significant elevation in SGPT measured 24 hours post exposure (Gehring, 1968). In comparison to the hepatotoxins, carbon tetrachloride and chloroform, 1,1,2-trichloroethane was judged a moderate hepatotoxin based on SGPT elevation.

Twenty-four hours after the administration of a subacute oral dose of 1,1,1,2-tetrachloroethane to rabbits (0.5 g/kg body weight), the activity of enzymes indicating hepatoxicity (SGPT, SGOT, LDH and α-hydroxy-butyrate dehydrogenase) was enhanced (Truhaut, et al. 1973), and remained enhanced 72 hours after poisoning. Blood cholesterol and total lipid levels were also increased.

Acute exposures by inhalation to vapor of 1,1,2,2-tetrachloroethane produced anesthesia, death, fatty degeneration of the liver, and tissue congestion in mice (Muller, 1932; Horiguchi, et al. 1962) and rats (Horiguchi, et al. 1962). Exposure concentrations ranged from 5,900 ppm (three hours) to 11,400 ppm (six hours, two days). In monkeys exposed to 1,000 ppm or 4,000 ppm, two hours/day for 190 days, marked vacuolation of the liver was observed (Horiguchi, et al. 1962). A single four-hour exposure of rats to 1,000 ppm of the compound caused the death of three of six animals in 14 days (Smyth, et al. 1969). A three-hour exposure of mice to 600 ppm increased hepatic triglycerides and total lipids and decreased hepatic energy stores (Tomokuni, 1969).

Intravenous (i.v.) or intraperitoneal (i.p.) injection of 1,1,2,2-tetrachloroethane (total of 0.7 ml in five doses in 14 days) in guinea pigs caused weight loss, convulsions, death, and fatty degeneration of the liver and kidney (Muller, 1932). Two-tenths of a gram administered i.v. to rabbits was lethal in 30 hours (Muller, 1932). In mice, i.p. injection of 200 mg/kg was lethal in seven days (Natl. Res. Counc., 1952). Plaa and Larson (1965) reported death of nine of ten mice and increased urinary protein and glucose in the survivor resulting from the i.p. injection of 1.6 g/kg of the compound in corn oil on three alternate days.

Chronic exposures of rabbits by inhalation to 1,1,2,2-tetrachloroethane (14.6 ppm, four hours/day for 11 months) induced liver and kidney degeneration (Navrotskiy, et al. 1971). Inhalation by rats of 1.94 ppm, four hours/day up to 265 days, increased the number of white blood cells, pituitary adrenocorticotropic hormone, and the total fat content of the liver (Deguchi, 1972).

A number of human deaths have resulted from accidental or intentional 1,1,2,2-tetrachloroethane ingestion (Hepple, 1927; Elliot, 1933; Forbes, 1943; Lilliman, 1949; Lynch, 1967). In cases of occupational poisoning, effects of 1,1,2,2-tetrachloroethane have included dizziness, vomiting, malaise, headache, hand tremors, and abdominal pain (Lehmann and Schmidt-Kehl, 1936; Horiguchi, et al. 1962; Lobo-Mendonca, 1963; Wilcox, et al. 1915). Four deaths have been attributed to industrial exposure to 1,1,2,2-tetrachloroethane (Wilcox, et al. 1915).

Acute testing in laboratory animals indicated that hexachloroethane was moderately toxic when administered orally (Weeks, et al. 1979). The compound was dissolved in corn oil (50 percent, weight/volume) or methylcellulose (five percent, weight/volume) and administered by stomach tube to male and female rats and male guinea pigs. Following a 14-day observation period, the oral LD_{50} for male rats was 5,160 mg/kg in corn oil and 7,690 mg/kg in methylcellulose; in female rats, the oral LD_{50} values were 4,460 and 7,080 mg/kg. In guinea pigs, the oral LD_{50} in corn oil was 4,970 mg/kg.

Daily oral doses (12 days) of hexachloroethane of 1,000 or 320 mg/kg administered to rabbits produced liver degeneration and toxic tubular nephrosis of the kidney. Animals were necropsied four days after the last exposure. Liver or kidney degeneration was not observed in rabbits receiving 100 mg/kg (Weeks, et al. 1979).

Exposure of dogs, guinea pigs, and rats by inhalation to 260 ppm hexachloroethane for six hours per day, five days/week for six weeks produced central nervous system toxicity in dogs and rats, and significantly higher liver-to-body weight ratios in guinea pigs and female rats. In male rats, the kidney-, spleen-, and testes-to-body ratios were significantly higher than controls. Half of the animals were sacrificed at the end of exposure and the remainder 12 weeks later. Evaluation of animals exposed to 48 ppm or 15 ppm revealed no adverse effects related to hexachloroethane exposure (Weeks, et al. 1979).

Laboratory animals (Table 16) and humans (Table 17) exposed to chloroethanes show similar symptoms of toxicity including eye and skin irritations, liver, kidney, and heart degeneration, and central nervous system depression.

Based on data derived from animal studies, the relative toxicity of chloroethanes is: 1,2-dichloroethane > 1,1,2,2-tetrachloroethane > 1,1,2-trichloroethane > hexachloroethane > 1,1-dichloroethane > 1,1,1-trichloroethane > monochloroethane. Available data are not sufficient to judge the relative toxicity of 1,1,1,2-tetrachloroethane or pentachloroethane.

Synergism and/or Antagonism

Pretreatment of mice with acetone or isopropyl alcohol (2.5 ml/kg, by gavage) enhanced the effects of threshold doses of 1,1,2-trichloroethane and produced an increased hepatotoxic response as measured by an increase in SGPT activity (Traiger and Plaa, 1974). Eighteen hours after pretreatment, the chlorinated hydrocarbon in corn oil was administered i.p.; 24 hours later, blood samples were taken by cardiac puncture. SGPT activity was not enhanced by 0.1 mg/kg 1,1,2-trichloroethane alone, but administration of acetone or isopropyl pretreatment, produced a significant increase in SGPT

TABLE 16

Adverse Effects of Chloroethanes Reported in Animal Studies*

Chemicals	Species	Adverse Effect
monochloroethane	unspecified	kidney damage; fatty changes in liver, kidney and heart
1,1-dichloroethane	cat	kidney damage
	dog	liver injury
	rat	liver injury; retarded fetal development
1,2-dichloroethane	bacterium	mutagen
	cat	retarded growth rate, fatty changes in liver; heart dilation; lung hyperemia
	dog	corneal clouding; fatty changes in liver; liver enlargement; weight loss
	fruit fly	mutagen
	guinea pig	fatty changes in liver; liver enlargement; weight loss
	monkey	fatty changes in liver
	rabbit	fatty changes in liver; hypotension; respiratory paralysis; EKG changes; anemia; bone marrow changes; liver dysfunction, hemorrhage and degeneration; kidney degeneration and dysfunction
	rat	embryotoxin; pulmonary congestion; fatty changes in liver
1,1,1,-trichloroethane	cat	neuromuscular reflex changes
	dog	sudden death; respiratory failure
	guinea pig	fatty changes in liver; lung irritation
	mouse	cardiac arrythmias; liver dysfunction; pulmonary congestion
	monkey	cardiac arrythmias; myocardial depression; respiratory failure; staggering gait; tachycardia; tremors
	rat	cardiac failure; pulmonary congestion; pneumonitis; staggering gait; weakness; semiconciousness; respiratory failure
1,1,2-trichloroethane	dog	liver and kidney injury
	guinea pig	liver and kidney injury
1,1,1,2-tetrachloroethane	rabbit	embryotoxin
	rat	embryotoxin; liver dysfunction; mutagen
1,1,2,2-tetrachloroethane	bacterium	mutagen
	dog	ascites; diarrhea; jaundice; liver enlargement; intestinal hemorrhage
	guinea pig	convulsions, weight loss; death
	monkey	anorexia; diarrhea; blood cell fluctuation; weight loss
	mouse	staggering gait; breathing difficulty; fatty degeneration of liver and kidney; death
	rabbit	altered immune system; altered blood chemistry; liver and kidney degeneration; fatty degeneration of liver and kidney; corneal reflex changes; liver enlargement; paralysis; death
	rat	blood cell changes; fatty degeneration of liver; liver dysfunction; death
pentachloroethane	cat	liver, kidney, and lung changes
	dog	fatty degeneration of liver; kidney and lung injury
	sheep	liver dysfunction
hexachloroethane	cattle	liver and kidney damage
	mouse	liver and kidney damage
	rat	liver and kidney damage
	sheep	liver and kidney damage

*Source: NIOSH, 1978c.

TABLE 17

Summary of Human Toxicity, Chloroethanes*

Chemical	System	Adverse Effect
monochloroethane	neurologic	central nervous system depression, headache, dizziness, incoordination feeling inebriated, unconsciousness
	gastrointestinal	abdominal cramps
	respiratory	respiratory tract irritation, respiratory failure
	cardiovascular	cardiac arrhythmias, cardiac arrest
	dermatological	skin irritation, frostbite, allergic eczema
	other	eye irritation, death
1,1-dichloroethane	neurologic	central nervous system depression
	respiratory	respiratory tract irritation
	dermatologic	skin burn
1,2-dichloroethane	neurologic	headache, dizziness, unconsciousness, vertigo, hand tremors, generalized weakness, sleepiness, nervousness, mental confusion
	hepatic	liver function abnormalaties, cellular damage, toxic chemical hepatitis, jaundice, liver enlargement
1,1,1-trichloroethane	neurologic	central nervous systme depression, headache, dizziness, incoordination, feeling inebriated, unconsciousness; impaired perceptual speed, manual dexterity and equilibrium; increased reaction time, lightheadedness, drowsiness, sleepiness, generalized weakness, ringing sound in ears, unsteady gait, burning and/or prickling sensation in hands and/or feet
	hepatic	cellular damage, liver function abnormalities
	gastrointestinal	nausea, vomiting, diarrhea
	cardiovascular	drop in blood pressure (hypotension), decrease in heart rate (bradycardia), cardiac arrhythmias
	hematologic	blood clotting, scaliness, inflammation
	other	eye irritation, fatigue, death
1,1,2-trichloroethane		NIOSH is unaware of reports of adverse occupational exposure
1,1,1,2-tetrachloroethane		NIOSH is unaware of reports of adverse occupational exposure

TABLE 17 (continued)

Chemical	System	Adverse Effect
1,1,2,2-tetrachloroethane	neurologic	central nervous system depression, headache, feeling inebriated, unconsciousness, drowsiness, unsteady gait, vertigo, hand tremors, numbness in limbs, prickling sensation of fingers and toes, pain in soles of feet, loss of knee jerk, paralysis of some muscles of the hands and feet, inflammation of the peripheral nerves, slight paralysis of the soft palate, loss of the gag reflex, irritability, mental confusion, delirium, convulsions, stupor, coma
	hepatic	liver function abnormalities, massive cell damage, toxic chemical hepatitis, jaundice, liver enlargement, sensation of pressure in the liver area
	gastrointestinal	abdominal pain, nausea, vomiting, unpleasant taste in the mouth, loss of appetite (anorexia), vomiting of blood (hematemesis), increased flatulence, diarrhea, constipation, pale stools
	urologic	kidney damage, presence of bile pigments, albumen, and casts in the urine
	respiratory	excessive fluid in the lungs (pulmonary edema), respiratory paralysis
	cardiovascular	fatty degeneration of the heart muscle
	hematologic	anemia, increase in white cells, (and blood platelets)
	dermatologic	dryness, cracking, scaliness, inflammation, purpuric rash
	other	insomnia, general malaise, fatigue, excessive sweating, weight loss
pentachloroethane		NIOSH is unaware of reports of adverse occupational exposure
hexachloroethane	neurologic	inability to close eyelid; eye irritation, tearing of eyes, inflammation delicate membrane lining the eye, visual intolerane to light, (photophobia)

*Source: NIOSH, 1978c

activity. The hepatotoxicity of 1,1,1-trichloroethane was not altered by pretreatment with acetone or isopropyl alcohol in these experiments.

Pretreatment of mice for three days with ethanol (5 g/kg, by gavage) enhanced 1,1,1-trichloroethane-induced sulfobromophthalein (BSP) retention, an indicator of liver dysfunction (Klaassen and Plaa, 1966). The chlorinated hydrocarbon administered on day four (2.75 ml/kg, i.p.) increased BSP retention from 0.91 to 3.76 mg/100 ml. The effect of 1,1,2-trichloroethane on BSP retention was not potentiated by prior ingestion of ethanol. Cornish and Adefuin (1966) pretreated rats with ethanol which altered 1,1,1-trichloroethane hepatotoxicity as judged by SGOT activity. Pretreatment of rats with phenobarbital (i.p.) did not alter the effect of 1,1,1-trichloroethane on SGOT activity (Cornish, et al. 1973).

Exposure of rats to 3,000 ppm 1,1,1-trichloroethane for 24 hours decreased drug-induced sleeping times when followed by i.p. administration of hexobarbital, meprobamate, or zoxazolamine 24 hours post-exposure. Inhibitors of protein synthesis blocked the effect of 1,1,1-trichloroethane on hexobarbital-induced sleeping time (Fuller, et al. 1970). The hypothesis that hepatic microsomal enzymes were induced by the chlorinated hydrocarbon was supported by data showing in vitro stimulation of microsomal aniline hydroxylase activity by 1,1,1-trichloroethane (Van Dyke and Rikans, 1970).

Potentiation of toxicity was not observed in extensive studies with a mixture of 1,1,1-trichloroethane (75 percent) and tetrachloroethylene (25 percent) (by weight) in mice, rats, guinea pigs, rabbits, dogs, and human subjects (Rowe, et al. 1963).

Teratogenicity

No literature was found concerning the teratogenic effects of monochloroethane, 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane, 1,1,2,2-tetrachloroethane or pentachloroethane.

Inhalation of 1,1-dichloroethane (3,800 or 6,000 ppm) by pregnant rats seven hours per day on days 6 through 15 of gestation had no effect on the incidence of fetal resorptions, on fetal body measurements, or on the incidence of gross or soft tissue anomalies. A significantly increased incidence of delayed ossification of sternebrae was associated with exposure to 24,250 mg/m^3 1,1-dichloroethane which reflects retarded fetal development rather than a teratological effect (Schwetz, et al. 1974).

Female rats were exposed to 1,2-dichloroethane vapor (57 mg/m^3, 4 hrs/day, 6 days/week) for six months prior to breeding and throughout gestation. Litter size, number of live births, and fetal weights were reduced, as compared to nonexposed controls (Table 18). The first generation rats (exposed in utero) showed decreased viability; the females of the first generation exhibited prolonged estrus periods, and high perinatal mortality. Tissue and skeletal anomalies were not reported. Deviations or abnormalities in the development of the 2nd generation were not noted (Vozovaya, 1974).

Twenty-three pregnant Sprague-Dawley rats and 13 Swiss-Webster mice inhaled 4,740 mg/m^3 1,1,1-trichloroethane seven hours a day, from days 6 through 15 of gestation. There was no effect on

TABLE 18

Effect of 1,2-Dichloroethane on Fetal Rat Development*

Treatment	Litter Size	Percent Live Fetuses	Fetal Weight (g)
Filtered Air	9.7	94.9	6.44
1,2-dichloroethane[a]	6.5	76.9	5.06

*Source: Vozovaya, 1974

[a] 57 mg/m^3, 4 hrs/day, 6 days/week, throughout gestation

the average number of implantation sites per litter, litter size, the incidence of fetal resorptions, fetal sex ratios, or fetal body measurements among mice or rats (Dunnett test $p < 0.05$). Soft tissue and skeletal anomalies occurred in 1,1,1-trichloroethane-exposed animals which did not occur in control animals; however, the incidences were not statistically significant (Fisher Exact probability test, $p < 0.05$) (Schwetz, et al. 1975).

Pregnant Sprague-Dawley rats were treated from day 6 through day 16 of gestation with hexachloroethane administered either by inhalation (15, 48 or 260 ppm, 6 hours/day) or by stomach tube (50, 100 or 500 mg/kg/day). Dams receiving 500 mg/kg/day orally had a significantly lower number of live fetuses per litter and higher fetal resorption rates. Fetal parameters in all other groups were within normal limits. No significant skeletal or soft tissue anomalies resulted from hexachloroethane exposures (Weeks, et al. 1979).

Mutagenicity

No data were found in the literature regarding the mutagenic potential of monochloroethane or pentachloroehtane. Negative data has been found with several others. 1,1-Dichloroethane, 1,1,2-trichloroethane, and 1,1,1,2-tetrachloroethane were not mutagenic in the Ames *Salmonella*/microsome assay (Simmon, et al. 1977; Rannug, et al. 1978; Fishbein, 1979). Hexachloroethane was not mutagenic for five strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 1538, and TA 100) or one strain of yeast *(Saccharomyces cervisiae* D4) in the absence or presence of induced rat liver S-9 preparation (Weeks, et al. 1979).

Several of the chlorinated ethanes have given positive results. 1,1,1-Trichloroethane was tested for mutagenic activity using the Ames Salmonella/microsome assay; the test was conducted in a desiccator because of the compounds' volatility. 1,1,1-Trichloroethane was weakly mutagenic to Salmonella typhimurium strain TA 100 (Simmon, et al. 1977; Fishbein, 1979)

1,1,2,2-Tetrachloroethane and 1,2-dichloroethane were found to be moderately and weakly mutagenic, respectively, to DNA polymerase-deficient E. coli (E. coli pol A^+/pol A_1^-), and to S. typhimurium strains TA 1530 and TA 1535, but not to TA 1538 (Brem, et al. 1974; Rosenkranz, 1977). Rosenkranz (1977) states that in E. coli pol A^+/pol A^- and S. typhimurium systems 1,1,2,2-tetrachloroethane is more mutagenic than 1,2-dichloroethane.

Without metabolic activation, 1,2-dichloroethane is a weak mutagen in tester strains of S. typhimurium and DNA polymerase-deficient E. coli (Brem, et al. 1974; McCann, et al. 1975; Fishbein, 1976; Rosenkranz, 1977). The mutagenic activity of 1,2-dichloroethane was not enhanced using NADPH (Rannug and Ramel, 1977), liver microsomes (Rannug, et al. 1978), or standard rat liver S-9 mix (McCann, et al. 1975).

Rannug, et al. (1978) showed that the mutagenic activity of 1,2-dichloroethane could be greatly enhanced through metabolic activation with a factor in the soluble liver fraction (115,000 g supernatant). This activation is not microsomal and not dependant on NADPH. This was thought to indicate activation through conjugation with glutathione (Rannug and Beije, 1979). Rannug and Beije (1979) combined S. typhimurium strains TA 1530 and TA 1535 with isolated perfused rat liver and tested for mutagenicity after treatment with 1,2-dichloroethane. The resultant bile, containing the glutathione/1,2-dichloroethane conjugates, was shown to be highly mutagenic. In the same study, mice treated *in vivo* with 1,2-dichloroethane also produced mutagenic bile (Rannug and Beije, 1979).

1,2-Dichloroethane also induced very significant increases in somatic mutation frequencies in *Drosophilia melanogaster* (Nylander, et al. 1978). Morphological and chlorophyll mutations in eight varieties of peas were found after treatment of seeds with 1,2-dichloroethane (Kirichek, 1974).

Three possible metabolites of 1,2-dichloroethane, chloroethanol, chloroacetaldehyde, and chloroacetic acid, were compared with 1,2-dichloroethanol for mutagenic activity in *Salmonella* tester strains. On a molar basis, chloroacetaldehdye was much more mutagenic to strain TA 100 than were 1,2-dichloroethane, or chloroethanol; chloroacetic acid was inactive in this test (McCann, et al. 1975). Chloroacetaldehyde was also found to be mutagenic in *S. typhimurium* strains TA 1530 and TA 1535 (Rannug, et al. 1978). A conjugation product of 1,2-dichloroethane, S-chloroethyl cystein, proved to be more mutagenic than the parent compound (Rannug, et al. 1978).

In summary, no mutagenicity data are available in the literature concerning monochloroethane or pentachloroethane. 1,1-Dichloroethane, 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane, and hexachloroethane are not mutagenic in *Salmonella* tester strains. 1,1,1-Trichloroethane, and unactivated 1,2-dichloroethane are weakly mutagenic in various studies. 1,1,2,2-Tetrachloroethane was shown to be moderately mutagenic to Salmonella typhimurium and E. coli. Metabolically active 1,2-dichloroethane is highly mutagenic in S. typhimurium, E. coli, and D. melanogaster.

Carcinogenicity

1,2-Dichloroethane: 1,2-Dichloroethane was one of 16 contaminants tested for carcinogenicity by Theiss, et al. (1977). The compound was injected intraperitoneally into 6 to 8 week old male strain A/st mice; tricaprylin was used as a vehicle. The experimental group consisted of 20 mice at each dosage level (20, 40 and 100 mg/kg in each injection). The mice were injected 3 times a week for 24 injections. The mice were sacrificed 24 weeks after the first injection and examined for lung tumors. The standard student t test was used to determine significance of frequency of tumors in the experimental group as compared to the control group. The author concluded that 1,2-dichloroethane produced an elevated frequency of tumors that was not statisically significant but that further carcinogenicity studies of this compound are warranted (Theiss, et al. 1977).

A bioassay of 1,2-dichloroethane for carcinogenic potential was conducted by the National Cancer Institute (NCI, 1978a). Technical grade 1,2-dichloroethane (impurities less than ten percent) in corn oil was administered by stomach tube to 50 male and 50 female animals of each test species (Osborne-Mendel rats and B6C3F1 mice) at two dosage levels, five days/week. Mice received continuous treatments for 78 weeks. Rats received continuous treatments for 35 weeks; from week 36 through week 78, periods of one week of no treatment were alternated with periods of four weeks of treatment. Dosage levels were manipulated during the experiment: the two initial dose levels for male and female rats were 100 and 50 mg/kg/day; doses were increased to 150 and 75 mg/kg/day, then decreased to initial levels. The high time-weighted average dose for rats was 95 mg/kg/day; while the low time-weighted average dose was 47 mg/kg/day. Male mice received initial high doses of 150 mg/kg/day and low doses of 75 mg/kg/day. These doses were raised to 200 and 100 mg/kg/day. The high time-weighted average dose was 195 mg/kg/day; the low was 97 mg/kg/day. Female mice received initial high doses of 250 mg/kg/day and low doses of 125 mg/kg/day. These doses were raised to 400 and 200 mg/kg/day, then decreased to 300 and 150 mg/kg/day. The high time-weighted average dose was 299 mg/kg/day; the low was 149 mg/kg/day. After 78 weeks of treatment, rats were observed either until death or for an additional 32 weeks; mice were observed an additional 12 or 13 weeks (NCI, 1978a).

Control groups consisted of 20 male and 20 female animals of each test species. Vehicle controls were treated with corn oil by stomach tube according to the treatment regimen of the test animals. Untreated controls were not intubated.

Treatment of rats and mice with 1,2-dichloroethane induced a number of benign and malignant neoplasms (Table 19).

The incidences of squamous cell carcinomas of the forestomach, subcutaneous fibromas, and hemangiosarcoma in male rats and the incidence of mammary adenocarcinomas in female rats were

TABLE 19

Summary of Neoplasms in Rats and Mice Ingesting 1,2-Dichloroethane for 78 Weeks*

Species	Sex	Dose	Total No. of animals with tumors/ no. animals examined Benign	Malignant	Metastases
Rat[a]	male	untreated	2	6	-
		corn oil	3	1	-
		47	7	15	1
		95	17	16	4
	female	untreated	12	6	1
		corn oil	7	-	-
		47	20	8	-
		95	18	25	2
Mouse[b]	male	untreated	-	2	-
		corn oil	-	4	1
		97	1	15	1
		195	15	22	1
	female	untreated	1	3	-
		corn oil	1	5	-
		149	12	26	6
		299	16	21	6

*Source: NCI, 1978a

[a] Compound administered in corn oil by stomach tube five days/week. Concentration is a time-weighted average expressed in mg/kg/day.

[b] Two control groups: 20 animals per group. Experimental groups: 50 animals at each dosage level.

significantly correlated with increased doses of 1,2-dichloroethane according to the Fisher exact test and the Cochran-Armitage test (Table 20).

In male and female mice treated with 1,2-dichloroethane, the incidence of alveolar/bronchiolar adenomas was statistically significant. The incidence of mammary adenocarcinomas and of endometrial tumors in female mice and the incidence of hepatocellular carcinomas in male mice were statistically positively correlated with treatment (Table 21; NCI, 1978a).

In an inhalation study in 1951, Spencer, et al. exposed Wistar rats to 200 ppm 1,2-dichloroethane for 7-hours per day for a total of 151 times. The study lasted 212 days, and no evidence of carcinogenicity was found (as cited in U.S. EPA, 1979).

1,1,1-Trichloroethane: NCI (1977) conducted a bioassay of 1,1,1-trichloroethane to determine potential carcinogenicity. Technical grade 1,1,1-trichloroethane (impurities: three percent p-dioxane, two percent unidentified) in corn oil was administered by stomach tube to 50 male and 50 female animals of each test species (Osborne-Mendel rats and B6C3F1 mice) at two dosage levels, five days/week for 78 weeks. During the experiment, doses for mice were increased from 4,000 and 2,000 mg/kg/day to 6,000 and 3,000 mg/kg/day. The high time-weighted average dose was 5,615 mg/kg/day; the low was 2,807 mg/kg/day. Doses for rats remained constant at 1,500 and 750 mg/kg/day. All surviving rats were killed at 117 weeks of age; surviving mice were killed at 95 weeks (NCI, 1977).

TABLE 20

Percent[a] of Rats with 1,2-Dichloroethane Induced Neoplasms*,[b]

Tumor Type	Male				Female			
	Vehicle Controls[c]		Experimental[d]		Vehicle Controls[c]		Experimental[d]	
	Pooled	Matched	Low Dose[e]	High Dose[f]	Pooled	Matched	Low Dose[e]	High Dose[f]
Squamous-cell carcinoma: Stomach	0	0	6	18	-	-	-	-
Hemangiosarcoma: Circulatory system	2	-	18	14	-	-	-	-
Fibroma: Subcutaneous	0	-	10	12	-	-	-	-
Adenocarcinoma: Mammary gland	-	-	-	-	2	0	2	36

*Source: NCI, 1978a

[a] percent: animals with tumors/animals examined x 100

[b] includes only neoplasms that were statistically correlated with 1,2-dichloroethane treatment.

[c] two types of control groups were used for statistical analysis: a vehicle control group (matched vehicle control) and a pooled vehicle control group which combined the vehicle controls from the studies of 1,2-dichcloroethane, 1,1,2-trichloroethane, and trichloroethylene. The pooled control rats were of the same strain, were housed in the same room, were tested concurrently for at least one year, and were diagnosed by the same pathologists. The untreated control group was not used for analysis of tumor incidence.

[d] experimental group: 50 animals at each dosage level

[e] The low time-weighted average dose: 47 mg/kg/day

[f] The high time-weighted average dose: 95 mg/kg/day

TABLE 21

Percent[a] of Mice with 1,2-Dichloroethane Induced Neoplasms*,[b]

Tumor Type	Male				Female			
	Vehicle Controls[c]		Experimental[d]		Vehicle Controls[c]		Experimental[d]	
	Pooled	Matched	Low Dose[e]	High Dose[f]	Pooled	Matched	Low Dose[g]	High Dose[h]
Alveolar/Bronchiolar Adenoma	0	0	2	31	3	5	14	31
Endometrial Sarcoma	-	-	-	-	0	0	4	6
Hepatocellular Carinoma	7	5	13	25	-	-	-	-

*Source: NCI, 1978a

[a] Percent: animals with tumors/animals examined x 100

[b] includes only neoplasms that were statistically correlated with 1,2-dichloroethane treatment

[c] Two types of control groups were used for statistical analysis: the vehicle control group (matched vehicle control) and the pooled vehical control group which combined the vehicle controls from the studies of 1,2-dichloroethane, 1,1,2-trichloroehtane, and trichloroethylene. The pooled control mice were of the same strain, were housed in the same room, were tested concurrently for at least one year, and were diagnosed by the same pathologists. The untreated control group was not used for analysis of tumor incidence.

[d] experimental group: 50 animals at each dosage level

[e] The low time-weighted average dose: 97 mg/kg/day

[f] The high time-weighted average dose: 195 mg/kg/day

[g] The low time-weighted average dose: 149 mg/kg/day

[h] The high time-weighted average dose: 299 mg/kg/day

Control groups consisted of 20 animals of each sex and species. Carbon tetrachloride was administered as the positive control.

There was a moderate depression of body weight in male and female rats and mice throughout the study. Male and female rats given 1,1,1-trichloroethane exhibited earlier mortality than the untreated controls. The statistical test for the dose-related trend was significant ($P<0.04$). Survival of mice was significantly decreased; in female mice there was a dose-related trend in the numbers surviving ($P=0.002$). Fewer rats receiving 1,1,1-trichloroethane survived at both 78 and 110 weeks than did positive control rats receiving carbon tetrachloride, a known carcinogen (Table 22). Chronic murine pneumonia was the most probable cause for the high incidence of deaths in several groups.

Although a variety of neoplasms was observed in both 1,1,1,-trichloroethane-treated and matched-control rats and mice (Table 23), no relationship was established between dosage groups, species, sex, type of neoplasm, or site of occurrence. The shortened life-spans of the rats and mice made an assessment of ingested 1,1,1-trichloroethane carcinogenicity impossible (NCI, 1977). The National Cancer Institute is currently retesting the compound.

Price, et al. (1978) demonstrated the in vitro transforming potential of 1,1,1-trichloroethane (99.9 percent pure) using the Fischer rat embryo cell system (F1706). Rat embryo cell cultures were treated with 1,1,1-trichloroethane, diluted in growth medium, for 48 hours. After nine subcultures, the transformed cells

TABLE 22

Comparison of Survival of Control Groups, 1,1,1-Trichloroethane-Treated and Carbon Tetrachloride-Treated (Positive Control) Rats*

Group	1,1,1-Trichloroethane			Carbon Tetrachloride		
	Initial No. of Animals	Number Alive at 78 weeks	Number Alive at 110 weeks	Initial No. of Animals	Number Alive at 78 weeks	Number Alive at 110 weeks
Male						
Control	20	7	0	20	20	12
Low Dose	50	1	0	50	34	15
High Dose	50	4	0	50	35	8
Female						
Control	20	14	3	20	18	14
Low Dose	50	9	2	50	38	20
High Dose	50	12	1	50	21	14

*Source: NCI, 1977

TABLE 23

Summary of Neoplasms in Rats and Mice Ingesting 1,1,1-Trichloroethane for 78 Weeks*

Species	Sex	Number of Animals	Dose[a]	Total Number of Tumors	Number of Tumors Observed						
					Liver, Spleen	Lung	Kidney, Bladder	Skin	Heart Vasculature	Brain, Pituitary	Other
Rat	Male	20	-	3	1	-	-	1	-	-	1
		50	750	6	1	-	-	-	1	1	3
		50	1500	4	-	-	1	-	1	-	3
	Female	20	-	14	-	-	-	-	-	3	11
		50	750	6	-	-	-	-	-	2	4
		50	1500	12	1	-	-	1	1	1	8
Mouse	Male	20	-	5	2	1	-	-	-	-	2
		50	2807	2	1	1	-	-	-	-	-
		50	5615	9	8	1	-	-	-	-	-
	Female	20	-	5	2	-	2	-	-	1	5
		50	2807	2	1	-	-	1	-	-	-
		50	5615	3	-	1	-	1	-	-	1

*Source: NCI, 1977

[a] Compound administered in corn oil by stomach tube five days per week. Concentration is a time-weighted average expressed in mg/kg/day.

(characterized by morphology and formation of macroscopic foci in semi-soft agar) were inoculated into newborn Fischer rats. By 68 days, the transformed cells had grown as undifferentiated fibrosarcomas at the innoculation sites in all tested animals. Acetone, the negative control, did not induce tumors by 82 days after innoculation (Price, et al. 1978).

1,1,2-Trichloroethane: A bioassay of 1,1,2-trichloroethane for possible carcinogenicity was conducted by the NCI (1978b). Technical grade 1,1,2-trichloroethane (92.7 percent pure) in corn oil was administered by stomach tube to 50 male and 50 female animals of each test species (Osborne-Mendel rats and B6C3F1 mice) at two dosage levels, five days/week for 78 weeks. During the experiment, doses for rats were increased from 70 and 30 mg/kg/day to 100 and 50 mg/kg/day. The high time-weighted average dose was 92 mg/kg/day; the low was 46 mg/kg/day. Doses for mice were increased from 300 and 150 mg/kg/day to 400 and 200 mg/kg/day. The high time-weighted average dose was 390 mg/kg/day; the low was 195 mg/kg/day. After 78 weeks of treatment, rats were observed an additional 35 weeks; mice were observed for an additional 13 weeks (NCI, 1978b).

Control groups consisted of 20 animals of each sex and species. Vehicle controls were treated with corn oil by stomach tube at the same rate as the high dose group of the same sex; untreated control animals were not intubated.

Adrenal cortical carcinomas, transitional-cell carcinoma of the kidney, renal tubule adenoma, and hemangiosarcomas of the spleen, pancreas, abdomen, and subcutaneous tissue were some of the neoplasms observed in treated, but not control rats. Because a statistically significant difference could not be found between the test group and the controls, carcinogenicity of 1,1,2-trichloroethane in Osborne-Mendel rats cannot be inferred (Table 24; NCI, 1978b).

On the other hand, treatment of mice with 1,1,2-trichloroethane was correlated with an increased incidence of hepatocellular carcinoma (Table 25). Both the Fisher exact test comparing tumor incidences of dosed to control groups and the Cochran-Armitage test for positive dose-related trend established that this correlation was significant ($P < 0.001$). The Cochran-Armitage test also showed a significant dose-related association between 1,1,2-trichloroethane treatment and incidence of pheochromocytoma of the adrenal gland in male and female mice. Fisher exact tests, however, confirmed this association only for high dose female mice, not other mouse groups (NCI, 1978b).

1,1,2,2-Tetrachloroethane: Technical grade 1,1,2,2-tetrachloroethane (90 percent pure) in corn oil was administered by stomach tube to 50 male and 50 female animals of each test species (Osborne-Mendel rats and B6C3F1 mice) at two dosage levels, five days/week. Mice received continuous treatments for 78 weeks. Rats received continuous treatment for 32 weeks; from week 33 through week 78, periods of one week of no treatment were alternated with periods of four weeks of treatment. Dosage levels were manipulated during the experiment: the initial dosages for male and female rats were 100 mg/kg/day and 50 mg/kg/day; dosage levels for males were then increased to 130 mg/kg/day and 65 mg/kg/day. The high time-

TABLE 24

Summary of Incidence of Neoplasms in Rats and Mice Ingesting 1,1,2-Trichloroethane for 78 Weeks*

Species	Sex	Dose[a]	Total Number of Animals with Tumors		
			Benign	Malignant	Metastases
Rat[b]	Male	Untreated	1	3	1
		Corn Oil	3	5	-
		46	11	12	1
		92	4	8	-
	Female	Untreated	9	3	-
		Corn Oil	4	-	-
		46	29	6	-
		92	15	9	2
Mouse[b]	Male	Untreated	2	3	-
		Corn Oil	1	5	-
		195	6	27	-
		390	9	38	3
	Female	Untreated	1	3	-
		Corn Oil	-	4	-
		195	4	18	-
		390	16	40	3

*Source: NCI, 1978b

[a] Compound administered in corn oil by stomach tube five days/week. Concentration is a time-weighted average expressed in mg/kg/day.

[b] Two control groups: 20 animals per group
Experimental groups: 50 animals per dosage level

TABLE 25

Incidence of Hepatocellular Carcinoma In Mice Ingesting 1,1,2-Trichloroethane for 78 Weeks*

Sex	Dose[a]	Number of Animals Examined	Hepatocellular Carcinoma	
			No. of Animals	Percent
Male[b]	Untreated	17	2	12
	Corn Oil	20	2	10
	195	49	18	37
	390	49	37	76
Female[b]	Untreated	20	2	10
	Corn Oil	20	0	--
	195	48	16	33
	390	45	40	89

*Source: NCI, 1978b

[a] Compound administered in corn oil by stomach tube five days/week. Concentration is a time-weighted average expressed in mg/kg/day.

[b] Two control groups: 20 animals per group. Experimental groups. 50 animals per dosage level.

weighted average dose for male rats was 108 mg/kg/day; the low was 62 mg/kg/day. For female rats, the high time-weighted average dose was 76 mg/kg/day and the low was 43 mg/kg/day. The initial dose for male and female mice was 200 mg/kg/day. This high dose was first increased to 300 mg/kg/day, then to 400 mg/kg/day, and finally lowered to 300 mg/kg/day. The initial low dose for both sexes was 100 mg/kg/day. The low dose was increased to 150 mg/kg/day. The high time-weighted average dose for male and female mice was 282 mg/kg/day; the low was 142 mg/kg/day. After 78 weeks of treatment, rats were observed for an additional 32 weeks and mice for an additional 12 weeks (NCI, 1978c).

Control groups consisted of 20 animals of each sex and species. Vehicle controls were treated with corn oil by stomach tube; untreated controls were not intubated.

The incidence of hepatocellular carcinoma in male and female mice was positively correlated ($P < 0.001$) with dosage level (Table 26). The incidence of total neoplasms in male and female mice is seen in Table 27. Although one neoplastic nodule and two hepatocellular carcinomas, rare tumors in the Osborne-Mendel rat, were seen in high dose male rats, the incidence of neoplasms in rats of either sex was not statistically significant (Table 27; NCI, 1978c).

Hexachloroethane: Technical grade hexachloroethane (98 percent pure) in corn oil was administered by stomach tube to 50 male and 50 female animals of each test species (Osborne-Mendel rats and B6C3F1 mice) at two dosage levels, five days/week. Mice received continuous treatments for 78 weeks. Rats received

TABLE 26

Incidence of Hepatocellular Carcinoma in Mice Ingesting 1,1,2,2-Tetrachloroethane[a] for 78 Weeks*

Sex	Dose[b]	Number of Animals Examined	Hepatocellular Carcinoma	
			Number	Percent
Male[c]	Untreated	16	2	13
	Corn Oil	18	1	6
	142	50	13	26
	282	49	44	90
Female[c]	Untreated	18	0	--
	Corn Oil	20	0	--
	142	48	30	63
	282	47	43	91

*Source: NCI, 1978c

[a] Incidence of hepatocellular carcinoma indicated a highly significant ($P < 0.001$) positive dose-related trend in mice of both sexes.

[b] Compound administered in corn oil by stomach tube five days/week. Concentration is a time-weighted average expressed in mg/kg/day.

[c] Two control groups: 20 animals per group.
Experimental groups: 50 animals per dosage level.

TABLE 27

Summary of Incidence of Neoplasms in Rats and Mice Ingesting 1,1,2,2-Tetrachloroethane for 78 Weeks*

Species	Sex	Dose[a]	Total Number of Animals with Tumors		
			Benign	Malignant	Metastases
Rat[b]	Male	Untreated	2	6	-
		Corn Oil	9	6	-
		62	11	7	1
		108	13	9	-
	Female	Untreated	12	6	1
		Corn Oil	11	1	-
		43	24	7	1
		76	21	5	-
Mouse[b]	Male	Untreated	2	9	-
		Corn Oil	3	1	-
		142	3	17	1
		282	3	45	-
	Female	Untreated	1	1	-
		Corn Oil	-	1	1
		142	2	33	-
		282	2	43	-

*Source: NCI, 1978c

[a] Compound administered in corn oil by stomach tube five days/week. Concentration is a time-weighted average expressed in mg/kg/day.

[b] Two control groups: 20 animals per group. Experimental groups: 50 animals per dosage level.

continuous treatments for 22 weeks; from week 23 through week 78, periods of one week of no treatment were alternated with periods of four weeks of treatment. Male and female rats received high doses of 500 mg/kg/day and low doses of 250 mg/kg/day. Although dosage levels remained constant throughout the study, treatment was not continuous: the high and low time-weighted average doses for rats were 432 and 212 mg/kg/day. Male and female mice received initial high doses of 1,000 mg/kg/day and low doses of 500 mg/kg/day. The doses were increased to 1,200 mg/kg/day and 600 mg/kg/day. The high time-weighted average dose was 1,179 mg/kg/day; the low time-weighted average dose was 590 mg/kg/day (NCI, 1978d). After 78 weeks of treatment, rats were observed for an additional 33 or 34 weeks, mice for an additional 12 or 13 weeks.

Control groups consisted of 20 animals of each sex and test species. Vehicle controls were treated with corn oil by stomach tube; untreated animals were not intubated.

Toxic tubular nephropathy was observed in all groups of treated animals: in rats, the incidence was 18 to 66 percent, and in mice, 92 to 100 percent. Male and female rats exhibited increased mortality rates which were statistically correlated with increased dosage. This trend was not evident with mice of either sex (NCI, 1978d).

In mice of both sexes, the incidence of hepatocellular carcinoma was positively correlated ($P < 0.001$) with hexachloroethane treatment (Table 28). There was no evidence of hexachloroethane induced neoplasms in rats of either sex (Table 29; NCI, 1978d).

TABLE 28

Incidence of Hepatocellular Carcinoma in Mice Ingesting Hexachloroethane for 78 Weeks*

Sex	Dose[a]	Number of Animals Examined	Hepatocellular Carcinoma No. of Animals	Hepatocellular Carcinoma Percent
Male[b]	Untreated	18	1	6
	Corn Oil	20	3	15
	590	50	15	30
	1179	49	31	63
Female[b]	Untreated	18	0	0
	Corn Oil	20	2	10
	590	50	20	40
	1179	49	15	31

*Source: NCI, 1978d

[a] Compound administered in corn oil by stomach tube five days/week. Concentration is a time-weighted average expressed in mg/kg/day.

[b] Two control groups: 20 animals per group. Experimental groups: 50 animals per dosage level.

TABLE 29

Summary of Incidence of Neoplasms in Rats and Mice[a] Ingesting Hexachloroethane for 78 Weeks*

Species	Sex	Dose[a]	Total Number of Animals with Tumors		
			Benign	Malignant	Metastases
Rat[b]	Male	Untreated	6	5	-
		Corn Oil	7	4	1
		212	12	6	2
		423	8	1	-
	Female	Untreated	11	6	1
		Corn Oil	11	4	1
		212	29	6	1
		423	18	3	1
Mouse[b]	Male	Untreated	0	3	1
		Corn Oil	1	3	-
		590	1	16	1
		1179	5	33	-
	Female	Untreated	3	2	1
		Corn Oil	2	6	-
		590	3	31	1
		1179	4	24	-

*Source: NCI, 1978d

[a] Compound administered in corn oil by stomach tube five days/week. Concentration is a time-weighted average expressed in mg/kg/day.

[b] Two control groups: 20 animals per group. Experimental groups: 50 animals per group.

A summary of the results of the NCI bioassays of chloroethanes is presented in Table 30.

An estimated five million workers are potentially exposed to one or more chloroethanes (NIOSH, 1978c). To date, no epidemiological relationship has been found between chloroethane exposure and human cancer.

TABLE 30

Summary of National Cancer Institute Bioassay
Results as of July, 1978*

Compound	Species/Sex	Tumor Site	Statistically Significant Tumors
monochloroethane	no testing planned		
1,1-dichloroethane	retesting recommended because initial results inconclusive		
1,2-dichloroethane	rats/female	mammary gland	adenocarcinomas
	rats/male	forestomach	squamous cell carcinomas
		circulatory system	hemangiosarcomas
		subcutaneous tissue	fibromas
	mice/female	mammary gland	adenocarcinomas
		endometrium	stromal sarcomas
		lungs	adenomas
	mice/male	lungs	adenomas
1,1,1-trichloroethane	retesting in progress		
1,1,2-trichloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
	mice	adrenal glands	pheochromocytomas
1,1,1,2-tetrachloroethane	testing in progress, no report available		
1,1,2,2-tetrachloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
Pentachloroethane	testing in progress, no report available		
hexachloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas

*Source: NIOSH, 1978c

CRITERION FORMULATION

Existing Guidelines and Standards

OSHA standards and NIOSH recommended standards are based on exposure by inhalation (Table 31). Based on information available in 1976b, NIOSH recommended that occupational exposures to 1,2-dichloroethane should not exceed 5 ppm (20 mg/m^3) determined as a time-weighted average for up to a 10-hour work day, 40-hour work week. Peak concentrations should not exceed 15 ppm (60 mg/m^3) as determined by a 15-minute sample. The current enforced OSHA exposure standard is 50 ppm, time-weighted average for up to a 10-hour work day, 40-hour work week. NIOSH (1976b) issued a criterion for a recommended standard of 200 ppm for occupational exposures to 1,1,1-trichloroethane. This recommendation to change the standard from 350 ppm is based on central nervous system responses to acute exposures in man, cardiovascular and respiratory effects in man and animals, and the absence of reported effects in man at concentrations below the proposed limit.

Current Levels of Exposure

Estimates of human exposure to chloroethanes via ingestion are not available for the general population. NIOSH (1978c) estimated that of over five million workers exposed by inhalation and dermal routes to chloroethanes, 4.5 million are exposed to 1,2-dichloroethane or 1,1,1-trichloroethane (Table 32).

In the general population there are chronic exposures to variable amounts in air and finished water. Chloroethanes are

TABLE 31

Chloroethane Exposure Standards*

Chemical	OSHA Exposure Standard (ppm)	NIOSH Recommended Exposure Standard (ppm)
monochloroethane	1,000	none
1,1-dichloroethane	100	none
1,2-dichloroethane	50	5
1,1,1-trichloroethane	350	200
1,1,2-trichloroethane	10	none
1,1,1,2-tetrachloroethane	none	none
1,1,2,2-tetrachloroethane	5	1
pentachloroethane	none	**
hexachloroethane	1	**

*Source: NIOSH, 1978c

**NIOSH has tentative plans for a Criteria Document for a Recommended Standard for this substance

TABLE 32

Chloroethane Exposures and Production*

Chemical	Estimated number of workers exposed	Annual Production quantities (pounds)
monochloroethane	113,000	670 million (1976)
1,1-dichloroethane	4,600	b
1,2-dichloroethane	1,900,000	8 billion (1976)
1,1,1-trichloroethane	2,900,000	630 million (1976)
1,1,2-trichloroethane	112,000	c
1,1,1,2-tetrachloroethane	a	b
1,1,2,2-tetrachloroethane	11,000	c
pentachloroethane	a	b
hexachloroethane	1,500	b,d

*Source: NIOSH, 1978c

[a] NIOSH estimates not available

[b] Does not appear to be commercially produced in the United States

[c] Direct production information not available

[d] 730,000 kg were imported in 1976

present in many commercial products, and exposure of the population depends on the tendency of individuals to read and heed instructions.

Special Groups at Risk

Workers who are occupationally exposed to chloroethanes by inhalation and/or dermal absorption represent a special group at risk (Table 32). Epidemiological studies have not disclosed a relationship between exposure to chloroethanes and cancer; however, four chloroethanes have proved to be carcinogenic in at least one species of rodent (NCI, 1978a,b,c,d). Those individuals who are exposed to known hepatotoxins or have liver disease may constitute a group at risk. Sufficient data are not available to specifically identify other special groups at risk.

Basis and Derivation of Criteria

At the present time, there is insufficient mammalian toxicological information to establish a water criterion for human health for the following chloroethanes: monochloroethane, 1,1-dichloroethane, 1,1,1,2-tetrachloroethane and pentachloroethane. Available evidence indicates that the general population is exposed to only trace levels of 1,1-dichloroethane, 1,1,1,2-tetrachloroethane and pentachloroethane. Although inhalation exposure to monochloroethane is more widespread, it is considered one of the least toxic of the chloroethanes. Should significant levels of exposure be documented in the future, it will be necessary to conduct more extensive toxicological studies with these chloroethanes.

The criterion for 1,1,1-trichloroethane is based on toxic effects observed in the National Cancer Institute bioassay for possible carcinogenicity (1977). Results of the study showed that the survival of both Osborne-Mendel rats and B6C3F1 mice was significantly decreased in groups receiving oral doses of 1,1,1-trichloroethane. Chronic murine pneumonia may have been responsible for the high incidence of deaths. A variety of neoplasms was observed in both species; however, the incidence of specific malignancies was not significantly different from those observed in control animals. Survival time was significantly decreased in rats receiving the high dose, therefore, the criterion for 1,1,1-trichloroethane is based on the low dose in rats (750 mg/kg body weight, 5 days/week for 78 weeks) which produced toxic effects in a number of systems. It should be recognized that the actual no-observable-adverse-effect level (NOAEL) will be lower. However, use of the lowest-minimal-effect dose as an estimate of an "acceptable daily intake" has been practiced by the National Academy of Sciences (NAS, 1977). Thus, assuming a 70 kg body weight and using a safety factor of 1,000 (NAS, 1977) the following calculation can be derived:

$$\frac{750 \text{ mg/kg} \times 70 \text{ kg} \times 5/7 \text{ day}}{1000} = 37.5 \text{ mg/day}$$

Therefore, consumption of 2 liters of water daily and 6.5 grams of contaminated fish having a bioconcentration factor of 5.6, would result in, assuming 100 percent gastrointestinal absorption of 1,1,1-trichloroethane, a maximum permissible concentration of 18.4 mg/l for ingested water:

$$\frac{37.5 \text{ mg/day}}{2 \text{ liters} + (5.6 \times 0.0065) \times 1.0} = 18.4 \text{ mg/l}$$

In summary, based on the use of chronic rat toxological data and an uncertainty factor of 1,000, the criterion level of 1,1,1-trichloroethane corresponding to an acceptable daily intake of 37.5 mg/day, is 18.4 mg/l. Drinking water contributes 98 percent of the assumed exposure while eating contaminated fish products accounts for 2 percent. The criterion level can similarly be expressed as 1.03 g/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

Based on available literature, 1,1,2-tri-, 1,1,2,2-tetra-, and hexachloroethane are considered to be carcinogenic in at least one rodent species (NCI, 1978b,c,d). In the case of these three chloroethanes, a statistical evaluation of the incidences of hepatocellular carcinomas revealed a significant positive association between the administration of the respective chloroethanes and tumor incidence. It can be concluded that under the conditions of the NCI bioassay, 1,1,2-tri-; 1,1,2,2-tetra-; and hexachloroethane are carcinogenic in B6C3F1 mice, inducing (in all cases) hepatocellular carcinomas in either male or female mice. Ambient water criteria for these chloroethanes were calculated by applying a linearized multistage model, as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document to the results from the NCI bioassays found in Appendix I.

Under the conditions of an NCI (1978a) bioassay, 1,2-dichloroethane is also carcinogenic, inducing a statistically significant number of squamous cell carcinomas of the forestomach and hemangiosarcomas of the circulatory system in male rats, mammary adenocarcinomas in female rats and mice, and endometrial tumors in female mice. The criterion for 1,2-dichloroethane is also calculated by applying the linearized multistage model to data from the appropriate NCI bioassay found in Appendix I.

The criteria for chloroethanes is summarized in Table 33.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." 1,2-Dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane and hexachloroethane are suspected of being human carcinogens. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of these chlorinated ethanes in water for maxiumum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of these chlorinated ethanes corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, the U.S. EPA stated that it is

TABLE 33

Criteria for Chloroethanes

Compound	Criterion	Reference
Monochloroethane	None	
1,1-Dichloroethane	None	
1,2-Dichloroethane	9.4 ug/l - Carcinogenicity data	NCI, 1978a
1,1,1-Dichloroethane	18.4 mg/l - mammalian toxicity data	NCI, 1977
1,1,2-Trichloroethane	6.0 µg/l - Carcinogenicity data	NCI, 1978b
1,1,1,2-Tetrachloroethane	None	
1,1,2,2-Tetrachloroethane	1.7 µg/l - Carcinogenicity data	NCI, 1978c
Pentachloroethane	None	
Hexachloroethane	19 µg/l - Carcinogenicity data	NCI, 1978d

considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the following table.

Exposure Assumptions	Risk Levels and Corresponding Criteria (1)			
	0 µg/l	10^{-7} µg/l	10^{-6} µg/l	10^{-5} µg/l
2 liters of drinking water and consumption of 6.5 grams of fish and shellfish (2)				
1,2-dichloroethane	0	0.094	0.94	9.4
1,1,2-trichloroethane	0	0.06	0.6	6.0
1,1,2,2-tetrachloroethane	0	0.017	0.17	1.7
hexachloroethane	0	0.19	1.9	19
Consumption of fish and shellfish only				
1,2-dichloroethane	0	24.3	243	2,430
1,1,2-trichloroethane	0	4.18	41.8	418
1,1,2,2-tetrachloroethane	0	1.07	10.7	107
hexachloroethane	0	0.87	8.74	87.4

(1) Calculated by applying a linearized multistage model, as previously discussed, to the appropriate bioassay data presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Zero point four percent of 1,2-dichloroethane exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 1.2-fold. The remaining 99.6 percent of 1,2-dichloroethane exposure results from drinking water.

One point four percent of 1,1,2-trichloroethane exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 4.5-fold. The remaining 98.6 percent of 1,1,2-trichloroethane exposure results from drinking water.

One point six percent of 1,1,2,2-tetrachloroethane exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 5-fold. The remaining 98.4 percent of 1,1,2,2-tetrachloroethane exposure results from drinking water.

Seventy-eight percent of hexachloroethane exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 86.9-fold. The remaining 22 percent of hexachloroethane exposure results from drinking water.

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APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Chlorinated Ethanes*

Chlorinated ethanes are used extensively as solvents and as intermediates in chemical syntheses. They have been detected in U.S. drinking water supplies and in finished drinking water. Chlorinated ethanes, which have been detected in water, include 1,1- and 1,2-dichloroethanes, 1,1,1- and 1,1,2-trichloroethanes, and 1,1,1,2-tetrachloroethane.

Four of the nine chlorinated ethanes are known animal carcinogens. They are 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2,-tetrachloroethane and hexachloroethane (NCI, 1978a,b,c,d). Carcinogenesis testing of 1,1,1-trichloroethane (retesting), 1,1,1,2-tetrachloroethane and pentachloroethane is in progress at the National Cancer Institute (NCI). In November, 1979 carcinogenesis testing was planned to begin for chloroethane (NCI, 1979).

Chlorinated ethanes produce a variety of cancers in rats and mice, receiving oral doses of these chemicals. 1,2-Dichloroethane, administered by gavage over a period of 78 weeks, produced squamous cell carcinomas of the stomach and hemangiosarcomas in male Osborne-Mendel rats. None of the twenty control animals developed either cancer type. Female Osborne-Mendel rats and B6C3F1 mice developed adenocarcinomas of the mammary gland (NCI, 1978a).

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*This summary has been prepared and approved by the Carcinogens Assessment Group, EPA, on July 17, 1979.

Adenocarcinomas of the mammary gland were not observed in 20 vehicle-treated controls of both species.

1,1,2-Trichloroethane, administered by gavage over a period of 78 weeks induced hepatocellular carcinomas in male and female B6C3Fl mice (NCI, 1978b). Tumor incidences in treated males were 37/49 (76 percent) and 18/49 (37 percent) at the high and low doses respectively, as compared to 2/20 (10 percent) in the vehicle-treated controls. Tumor incidences in treated females were 40/45 (89 percent) and 16/48 (33 percent) at the high and low doses, respectively, as compared to no observed cancers in twenty vehicle controls.

1,1,1-Trichloroethane is being retested at the NCI because high mortality rates among animals, in an earlier carcinogenesis bioassay, made it impossible to assess the carcinogenicicty of ingested 1,1,1-trichloroethane, even though a variety of neoplasms were observed (NCI, 1977). In another study, 1,1,1-trichloroethane induced the transformation of rat embryo cells and the transformed cells, when injected into newborn Fischer rats, produced fibrosarcomas at the site of injection in all treated animals (Price, et al. 1978).

1,1,2,2-Tetrachloroethane is carcinogenic to B6C3Fl mice. This chemical, given by gavage, over a period of 78 weeks, induced hepatocellular carcinomas in male and female mice (NCI, 1978c). Tumor incidences in males were 44/49 (90 percent), 13/50 (26 percent), and 1/18 (5 percent) in the high dose, low dose, and vehicle control groups, respectively. Tumor incidences in females were

43/47 (91 percent), 30/48 (63 percent), and 0/20 in high dose, low dose, and vehicle control groups, respectively.

In addition to its use as a solvent, hexachloroethane is used as a veterinary anthelmitic. This chemical has demonstrated carcinogenic activity in both male and female B6C3F1 mice. Thirty-one of 49 (63 percent) and 15 of 50 (30 percent) treated male mice developed hepatocellular carcinomas after receiving high and low oral doses of hexachloroethane, respectively, over a 78-week period as compared to 3 of 20 vehicle-treated controls (15 percent). Twenty of 50 female mice (40 percent) developed hepatocellular carcinomas after receiving the high oral dose of hexachloroethane as compared to 2 of 20 (10 percent) vehicle-treated controls.

Three chlorinated ethanes are known mutagens. 1,1,1-Trichoroethane is weakly mutagenic to S. typhimurium strain TA 100 (Simmon, et al. 1977). 1,2-Dichloroethane and 1,1,2,2-tetrachloroethane were mutagenic in the Ames Salmonella assay for strains TA 1530 and 1535, and for the E. coli DNA polymerase-deficient system (Brem, et al. 1974). Rosenkranz (1977) determined the order of mutagenic activity toward S. typhimurium and E. coli to be 1,1,2,2-tetrachloroethane > 1,2-dichloroethane. 1,2-Dichloroethane induced highly significant increases in somatic mutation frequencies in Drosophila melangaster (Nylander, et al. 1978). Morphological and chlorophyll mutations in eight varietites of peas were induced by treatment of seeds with 1,2-dichloroethane (Kirichek, 1974).

A conjugation product of 1,2-dichloroethane, S-chloroethyl cystein, proved to be more mutagenic than the parent compound (Rannug, et al. 1978). Other metabolites of 1,2-dichloroethane varied in their mutagenic activity for Salmonella strains. 2-Chloroacetaldehyde was mutagenic for strain TA 100 (McCann, et al. 1975), strains TA 1530 and TA 1535 (Rannug, et al. 1978). 2-Chloroethanol was less mutagenic than the aldehyde derivative and 2-chloroacetic acid was inactive (McCann, et al. 1975).

1,1-Dichloroethane, 1,1,2-trichloroethane, and 1,1,1,2-tetrachloroethane were not mutagenic in the Ames Salmonella/microsome assay (Simmon, et al. 1977; Fishbein, 1979).

Hexachloroethane was not mutagenic for five strains of Salmonella or yeast (Sacchyaromyces cerevisiae D^4) in the absence or presence of induced rat liver S-9 preparations (Weeks, et al. 1979).

No data were found regarding the mutagenic potential of chloroethane, or pentachloroethane.

The demonstrated carcinogenicity of 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane and hexachloroethane coupled with the mutagenicity data constitutes strong evidence that these chemicals are likely to be human carcinogens.

The water quality criterion for 1,2-dichloroethane is based on the induction of circulatory system hemangiosarcomas in male Osborne-Mendel rats given oral doses of 1,2-dichloroethane over a period of 78 weeks (NCI, 1978a). The concentration of 1,2-dichloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5} is 9.4 μg/l.

The water quality criterion for 1,1,2-trichloroethane is based on the induction of hepatocellular carcinomas in male B6C3F1 mice given oral doses over a 78-week period (NCI, 1978b). The concentration of 1,1,2-trichloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5} is 6.0 µg/l.

The water quality crterion for 1,1,2,2-tetrachloroethane is based on the induction of hepatocellular carcinomas in female B6C3Fl mice, receiving oral doses over a 78-week period (NCI, 1978c). The concentration of 1,1,2,2-tetrachloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5} is 1.7 µg/l.

The water quality criterion for hexachloroethane is based on the induction of hepatocellular carcinomas in male B6C3Fl mice, given oral doses over a 78-week period (NCI, 1978d). The concentration of hexachloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5} is 19 µg/l.

Because carcinogenicity data are lacking for chloroethane, 1,1-dichloroethane, 1,1,1-trichloroethane, 1,1,1,2-tetrachloroethane, and pentachloroethane, water quality criteria based on a 10^{-5} risk level cannot be derived.

Summary of Pertinent Data for 1,2-Dichloroethane

The water quality criterion for 1,2-dichloroethane is based on the induction of circulatory system hemangiosarcomas in male Osborne-Mendel rats (NCI, 1978a). The incidences of these sarcomas along with other parameters of the extrapolation are listed below:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	0/20
33.6	9/50
67.9	7/50

le = 546 days
w = 0.500 kg
Le = 770 days
R = 1.2 l/kg
L = 770 days

With these parameters the carcinogenic potency factor for humans, q_1^*, is 3.697×10^{-2} $(\mathrm{mg/kg/day})^{-1}$. The concentration of 1,2-dichloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5} is 9.4 µg/l.

Summary of Pertinent Data for 1,1,2-trichloroethane

The water quality criterion for 1,1,2-trichloroethane is based on the induction of hepatocellular carcinomas in male B6C3F1 mice (NCI, 1978b). The incidences of hepatocellular carcinomas are listed below along with other parameters of the extrapolation:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	2/20
139	18/49
279	37/49

le = 546 days
w = 0.033 kg
Le = 637 days
R = 4.5 l/kg
L = 637 days

With these parameters the carcinogenic potency factor for humans, q_1^*, is 5.73×10^{-2} $(\text{mg/kg/day})^{-1}$. The concentration of 1,1,2-trichloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5} is 6.0 µg/l.

Summary of Pertinent Data for 1,1,2,2-Tetrachloroethane

The water quality criterion for 1,1,2,2-tetrachloroethane is based on the induction of hepatocellular carcinomas in female B6C3F1 mice (NCI, 1978c). The incidences of hepatocellular carcinomas are listed below as are additional parameters of the extrapolation:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	0/20
101	30/48
203	43/47

le = 546 days

Le = 637 days

L = 637 days

w = 0.030 kg

R = 5 l/kg

With these parameters the carcinogenic potency factor for humans, q_1^*, is 0.2013 $(mg/kg/day)^{-1}$. The concentration of 1,1,2,2-tetrachloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5}, is 1.7 µg/l.

Summary of Pertinent Data for Hexachloroethane

The water quality criterion for hexachloroethane is based on the induction of hepatocellular carcinomas in male B6C3F1 mice (NCI, 1978d). The incidences of hepatocellular carcinomas are listed below as are additional parameters used in the extrapolation:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	3/20
421	15/50
842	31/49

le = 546 days   w = 0.032 kg

Le = 637 days   R = 86.9 l/kg

L = 637 days

With these parameters the carcinogenic potency factor for humans, q_1^*, is 1.42×10^{-2} $(mg/kg/day)^{-1}$. The concentration of hexachloroethane in water, calculated to keep the lifetime cancer risk below 10^{-5}, is 19 µg/l.